* * * * *

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

* * * * *

Applicants: Solo Goldstein, et al.

Serial No.: 09/888,990

Filed : June 20, 2001

Title : "1,1-and 1,2-disubstituted cyclopropane compounds"

* * * * *

HON. COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

CLAIM TO PRIORITY AND FILING OF PRIORITY DOCUMENT
UNDER 37 CFR § 1.55 AND 35 USC § 119

Sir:

Herewith please find a certified copy of French priority application Serial No. 00.08203 filed June 27, 2000, and certified translation thereof into English, the right of priority of which was claimed upon filing of the above-identified application, and which claim is hereby repeated.

Respectfully submitted,
THE FIRM OF HUESCHEN & SAGE

By: G. PATRICK SAGE
G. PATRICK SAGE, ATTORNEY

Dated: October 5, 2001.

Customer No. 25,666
500 Columbia Plaza
350 East Michigan Ave.
Kalamazoo, MI 49007
(616) 382-0030

Enclosures: Certified copy of French priority application Serial No. 00.08203, certified translation thereof into English, and return postal card receipt.

CERTIFICATE OF MAILING UNDER 37 CFR 1.8(a)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on this date.

HUESCHEN AND SAGE

Dated: October 5, 2001

#3
M.M.
10/19/01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I, ADRIAN PAUL BROWN, M.A., M.I.L., M.I.T.I., declare

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland, residing at 5 Gilbert Road, London, SE11 4NZ.

2. That I am well acquainted with the French and English languages.

3. That the attached is a true translation into the English language of the certified copy of French Patent Application No. 00 08203 filed on 27th June 2000.

4. That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the patent application in the United States of America or any patent issuing thereon.

DECLARED THIS 10th DAY OF JULY 2001

A. P. Brown

ADRIAN PAUL BROWN

R E P U B L I C F R E N C H

INPI

NATIONAL INSTITUTE
FOR INDUSTRIAL
PROPERTY

PATENT OF INVENTION

UTILITY CERTIFICATE - CERTIFICATE OF ADDITION

OFFICIAL COPY

The Director General of the National Institute for Industrial Property certifies that the attached document is the true certified copy of an application for an Industrial Property Right filed at the Institute.

Issued in Paris, 6 MARCH 2001

For the Director General of the
National Institute for Industrial Property,
The Head of the Patents Division

(signature)

Martine PLANCHE

NATIONAL INSTITUTE FOR INDUSTRIAL PROPERTY

HEAD OFFICE
26 bis, rue de Saint Petersbourg
75800 PARIS cedex 08
Telephone: 01 53 04 53 04
Facsimile: 01 42 93 59 30
http://www.inpi.fr

NATIONAL PUBLIC INSTITUTION
CREATED BY LAW NO. 51-444 OF 19th APRIL 1951

INPI

National
Institute for
Industrial Property
26bis, rue de Saint Pétersbourg
75800 Paris Cedex 08
Telephone: 01 53 04 53 04
Facsimile: 01 42 94 86 54

PATENT OF INVENTION
UTILITY CERTIFICATE

Intellectual Property Code - Book VI

cerfa
No. 11354*01

REQUEST FOR GRANT 1/2

Reserved for INPI

This form is to be completed legibly in black ink DB 540 W /260899

DEPOSITION OF DOCUMENTS **DATE 27 JUNE 2000** **PLACE 75 INPI PARIS** **NATIONAL REGISTRATION NO. GIVEN BY THE INPI 0008203** **FILING DATE GIVEN BY THE INPI 27 JUNE 2000**	**1 NAME AND ADDRESS OF THE APPLICANT OR OF THE AUTHORISED AGENT TO WHOM CORRESPONDENCE MUST BE ADDRESSED** ADIR ET COMPAGNIE 1, rue Carle Hébert 92415 COURBEVOIE Cedex FRANCE
Your references for this file *(optional)* 35838	
Confirmation of a deposit by facsimile	☐ No. given by INPI to the facsimile

2 NATURE OF THE APPLICATION	**Mark one of the following 4 boxes**
Patent application	☒
Application for a Utility Certificate	☐
Divisional application	☐
Initial patent application	No. Date
or initial utility certificate application	No. Date
Conversion of a European Patent Application	☐
Initial patent application	No. Date

3 TITLE OF THE INVENTION (maximum 200 characters or spaces)

NEW 1,1- AND 1,2-DISUBSTITUTED CYCLOPROPANE COMPOUNDS, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM.

4 DECLARATION OF PRIORITY OR REQUEST FOR THE BENEFIT OF THE FILING DATE OF A PRIOR FRENCH APPLICATION	Country or organisation Date No. Country or organisation Date No. Country or organisation Date No. ☐ **If there are other priorities, mark the box and use the "Continuation" form**

5 APPLICANT		☐ **If there are other Applicants, mark the box and use the "Continuation" form**	
Name or company name		ADIR ET COMPAGNIE	
Forenames			
Legal nature			
SIREN No.			
APE-NAF Code			
Address	Street	1, rue Carle Hébert	
	Postal code and town	92415	COURBEVOIE CEDEX
Country		FRANCE	
Nationality		FRENCH	
Telephone no. *(optional)*		01.55.72.60.00	
Facsimile no. *(optional)*		01.55.72.72.13	
E-mail address *(optional)*			

INPI

National
Institute for
Industrial Property

PATENT OF INVENTION
UTILITY CERTIFICATE

REQUEST FOR GRANT 2/2

Reserved for INPI

DEPOSITION OF DOCUMENTS

DATE **27 JUNE 2000**

PLACE **75 INPI PARIS**

NATIONAL REGISTRATION NO.
GIVEN BY THE INPI **0008203**

DB 540 W /260899

Your references for this file: *(optional)*		35838
6 AUTHORISED AGENT		
Name		DERBOIS
Forename		Catherine
Practice or company		ADIR ET COMPAGNIE
No. of standing power of attorney and/or of contractual bond		
Address	Street	1, rue Carle Hébert
	Postal code and town	92415 COURBEVOIE CEDEX
Telephone no. *(optional)*		01.55.72.60.00
Facsimile no. *(optional)*		01.55.72.72.13
E-mail address *(optional)*		
7 INVENTOR(S)		
The inventors are the Applicants		☐ Yes ☒ No **In this case, supply a separate designation of inventorship**
8 SEARCH REPORT		**For a patent application only (including division and conversion)**
immediate drawing up		☒
or deferred drawing up		☐
Payment of the fees in instalments		**Payment in three instalments, for natural persons only** ☐ Yes ☐ No
9 REDUCTION IN FEES		**For natural persons only** ☐ Requested for the first time for this invention *(attach a notice of non-imposition)* ☐ Requested prior to this deposit *(attach a copy of the admissibility decision for this invention or indicate its reference)*
If you have used the "Continuation" form, indicate the number of pages attached		

10 SIGNATURE OF THE APPLICANT OR OF THE AUTHORISED AGENT **(Name and position of signatory)** [signature] Catherine DERBOIS, Patent Engineer	**STAMP OF THE PREFECTURE OR OF THE INPI** [signature]

Law No. 78-17 of 6 January 1978 relating to information processing, data files and rights applies to the responses made on this form. It guarantees right of access to and correction of the data concerning you at the INPI.

INPI

National
Institute for
Industrial Property

PATENTS DEPARTMENT
26bis, rue de Saint Pétersbourg
75800 Paris Cedex 08
Telephone: 01 53 04 53 04
Facsimile: 01 42 93 59 30

PATENT OF INVENTION
UTILITY CERTIFICATE

Intellectual Property Code - Book VI

cerfa
No. 11235*02

DECLARATION OF INVENTORSHIP

Page No. 1 /2

(if the applicant is not the inventor or not the only inventor)

This form is to be completed legibly in black ink DB 113 W /260899

Your references for this file *(optional)*	35838
NATIONAL REGISTRATION NO.	0008203

TITLE OF THE INVENTION (maximum 200 characters or spaces)

NEW 1,1- AND 1,2-DISUBSTITUTED CYCLOPROPANE COMPOUNDS, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM.

APPLICANT(S):

ADIR ET COMPAGNIE
1, rue Carle Hébert
92415 COURBEVOIE Cedex
FRANCE

DESIGNATE(S) AS INVENTOR(S) : (Indicate at the top right-hand side "Page No. 1/1". If there are more than three inventors, use an identical form and number each page indicating the total number of pages).

Name		GOLDSTEIN	
Forenames		Solo	
Address	Street	11, rue du Bac	
	Postal code and town	92150	SURESNES
Belonging company *(optional)*			
Name		GUILLONNEAU	
Forenames		Claude	
Address	Street	21, rue des Bergères	
	Postal code and town	92140	CLAMART
Belonging company *(optional)*			
Name		CHARTON	
Forenames		Yves	
Address	Street	9, allée Esterel	
	Postal code and town	92330	SCEAUX
Belonging company *(optional)*			

DATE AND SIGNATURE(S) OF THE APPLICANT(S) OR OF THE AUTHORISED AGENT (Name and position of signatory)	27 June 2000
Catherine DERBOIS, Patent Engineer	[signature]
(signature)	

INPI
National
Institute for
Industrial Property

PATENTS DEPARTMENT
26bis, rue de Saint Pétersbourg
75800 Paris Cedex 08
Telephone: 01 53 04 53 04
Facsimile: 01 42 93 59 30

PATENT OF INVENTION
UTILITY CERTIFICATE

Intellectual Property Code - Book VI

cerfa
No. 11235*02

DECLARATION OF INVENTORSHIP

Page No. 2 /2

(if the applicant is not the inventor or not the only inventor)

This form is to be completed legibly in black ink DB 113 W /260899

Your references for this file *(optional)*		35838	
NATIONAL REGISTRATION NO.		0008203	
TITLE OF THE INVENTION (maximum 200 characters or spaces)			
NEW 1,1- AND 1,2-DISUBSTITUTED CYCLOPROPANE COMPOUNDS, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM.			
APPLICANT(S):			
ADIR ET COMPAGNIE 1, rue Carle Hébert 92415 COURBEVOIE Cedex FRANCE			
DESIGNATE(S) AS INVENTOR(S) : (Indicate at the top right-hand side "Page No. 1/1". If there are more than three inventors, use an identical form and number each page indicating the total number of pages).			
Name		LOCKHART	
Forenames		Brian	
Address	Street	60, rue des Ponts	
	Postal code and town	78290	CROISSY SUR SEINE
Belonging company *(optional)*			
Name		LESTAGE	
Forenames		Pierre	
Address	Street	9, allée de la Grande Terre	
	Postal code and town	78170	LA CELLE SAINT CLOUD
Belonging company *(optional)*			
Name			
Forenames			
Address	Street		
	Postal code and town		
Belonging company *(optional)*			
DATE AND SIGNATURE(S) OF THE APPLICANT(S) OR OF THE AUTHORISED AGENT (Name and position of signatory) Catherine DERBOIS Patent Engineer (signature)		27 June 2000 [signature]	

The present invention relates to new 1,1- and 1,2-disubstituted cyclopropane compounds, to a process for their preparation and to pharmaceutical compositions containing them.

The compounds of the present invention are especially valuable from a pharmacological point of view because of their specific interaction with central nicotinic receptors of type $\alpha 4\beta 2$, having application in the treatment of neuropathologies associated with cerebral ageing, of mood disorders, of pain and of tobacco withdrawal.

Ageing of the population due to increased life expectancy at birth has brought with it a major increase in the incidence of age-related neuropathologies and especially of Alzheimer's disease. The principal clinical manifestations of cerebral ageing and especially of age-related neuropathologies are deficiencies in mnemic and cognitive functions, which may lead to dementia. It has been widely demonstrated that, of the various neurotransmitters, acetylcholine plays a major role in memory functions and that there is large-scale destruction of the cholinergic neuronal pathways in certain neurodegenerative diseases or when there is inadequate activation in the case of cerebral ageing. For that reason, numerous therapeutic approaches have been aimed at preventing destruction of the neurotransmitter by means of the inhibition of acetylcholinesterase or have sought to provide a substitute for the deficient neurotransmitter. In the latter case, the cholinergic agonists proposed have been of the muscarinic type, which are specific for post-synaptic M1 receptors.

It has recently been shown that the cholinergic impairment associated with Alzheimer's disease affects neurones carrying nicotinic receptors more than those carrying muscarinic receptors (Schroder *et al.*, "Alzheimer disease : therapeutic strategies", Birkhauser Boston, 1994, 181-185). Numerous studies have, moreover, demonstrated that nicotine has memory-facilitating properties (Prog. Neuropsychopharmacol., 1992, 16, 181-191) and that these properties are exerted as much on mnemic functions (Psychopharmacol., 1996, 123, 88-97) as on the faculties of attention and vigilance (Psychopharmacol., 1995, 118, 195-205). Furthermore, nicotine exerts neuroprotective effects with respect to excitotoxic agents such as glutamate (Brain Res., 1994, 644, 181-187).

All of these findings can very probably be linked with epidemiological studies which have shown a lower incidence of Alzheimer's disease and Parkinson's disease in smokers. Furthermore, several studies have shown the value of nicotine in the treatment of mood disorders such as states of depression, anxiety or schizophrenia. Finally, it has been shown that nicotine has antalgic properties. All of the therapeutic properties of nicotine and also those described for other nicotinic agents are based upon activity with respect to central receptors, which differ structurally and pharmacologically from peripheral receptors (muscle and ganglion) . The central receptors of type $\alpha 4\beta 2$ are the most represented in the central nervous system and have been implicated in the majority of the therapeutic effects of nicotine (Life Sci., 1995, 56, 545-570).

Several documents such as Synlett., 1999, 7, 1053-1054 ; J. Med. Chem, 1985, 28(12), 1953-1957 and 1980, 23(3), 339-341 ; 1970, 13(5), 820-826 ; 1972, 15(10), 1003-1006 ; J. Am. Chem. Soc., 1987, 109(13), 4036-4046, or a few patents or patent applications such as DE 36 08 727, EP 124 208 or WO 94/10158 describe and claim compounds containing a 1,1- or 1,2-disubstituted cyclopropane moiety. None of those references describe or suggest that those compounds have pharmacological activity that is specific for nicotinic receptors and more especially for central nicotinic receptors of type $\alpha 4\beta 2$, this being a novel property of the compounds described by the Applicant. Consequently, there is nothing in the prior art predicting the specific and surprising characteristics of the products claimed in the present Application.

The compounds of the present invention are therefore new and represent powerful selective nicotinic ligands of the central receptor sub-type $\alpha 4\beta 2$. They are consequently of use in the treatment of deficiencies of memory associated with cerebral ageing and with neuro-degenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease and frontal lobe and subcortical dementias, and also for the treatment of mood disorders, Tourette's syndrome, attention-deficit hyperactivity syndrome, tobacco withdrawal and pain.

More specifically, the present invention relates to compounds of formula (I) :

(I),

wherein :

p represents an integer of from 0 to 6 inclusive,

n represents an integer of from 0 to 6 inclusive,

R_1 and R_2, which may be identical or different, each independently of the other represent a group selected from a hydrogen atom, a linear or branched (C_1-C_6)alkyl group, an aryl group and an aryl-(C_1-C_6)alkyl group in which the alkyl moiety is linear or branched, or R_1+R_2 form together with the nitrogen atom carrying them a saturated, monocyclic or bicyclic (C_3-C_{10}) system, one of the carbon atoms of which is optionally replaced by a hetero atom selected from oxygen, nitrogen and sulphur,

X represents a group selected from an oxygen atom, a sulphur atom, a methylene group, a group of formula -HC=N-O- and a group of formula -O-CH_2-CH=CH-, in which groups the oxygen atom is linked to the Y moiety of the compounds of formula (I),

Y represents a group selected from aryl, heteroaryl, aryl-(C_1-C_6)alkyl in which the alkyl moiety is linear or branched, heteroaryl-(C_1-C_6)alkyl in which the alkyl moiety is linear or branched, -C(O)-A and -C(S)-A,

A represents a group selected from linear or branched (C_1-C_6)alkyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl in which the alkyl moiety is linear or branched, heteroaryl-(C_1-C_6)alkyl in which the alkyl moiety is linear or branched, and NR_3R_4 wherein R_3 and R_4, which may be identical or different, each represent a group selected from a hydrogen atom, a linear or branched (C_1-C_6)alkyl group, an aryl group and an aryl-(C_1-C_6)alkyl group in which the alkyl moiety is linear or branched, or R_3+R_4 form together with the nitrogen atom carrying them a monocyclic or bicyclic (C_3-C_{10}) system,

their isomers and addition salts thereof with a pharmaceutically acceptable acid or base,

with the proviso that :

• *in the case of 1,1-disubstituted compounds of formula (I),*

- p is other than zero when X represents a methylene group, n has the value zero, Y represents an aryl or heteroaryl group, and R_1 and R_2, which may be identical or different, represent a hydrogen atom, a linear or branched (C_1-C_4)alkyl group, a benzyl group, a

phenylethyl group, or form together with the nitrogen atom carrying them a morpholino group, a thiomorpholino group or a 5- to 7-membered saturated carbocyclic system,

- p is other than zero when X represents a methylene group, n has the value zero, Y represents an acetyl group, and R_1 and R_2, which may be identical or different, represent a hydrogen atom, a linear or branched (C_1-C_4)alkyl group, a phenyl group, a benzyl group, or form together with the nitrogen atom carrying them a piperidyl or morpholino group,
- R_1 and R_2 do not simultaneously represent a methyl group :
  * either when p and n each have the value 1, X represents an oxygen atom and Y represents a group selected from p-nitrobenzoyl, p-aminobenzoyl, p-chlorophenyl-aminocarbonyl or acetyl,
  * or when p has the value zero, n has the value 1, X represents an oxygen atom or a sulphur atom and Y represents a 2-quinolyl group substituted in the 3-position by a linear or branched (C_3-C_4)alkyl group, or a phenyl group,
- Y does not represent a 1,2-benzisoxazol-3-yl group when n has the value 1, p has the value zero and X represents an oxygen atom,

• *in the case of 1,2-disubstituted compounds of formula (I)*, R_1 and R_2 do not simultaneously represent a hydrogen atom when p and n each have the value zero and X-Y together represent a phenoxy group (optionally substituted by a methoxy group, a dimethylamino group, a fluorine atom or by one or two identical groups selected from a chlorine atom and a methyl group), a phenylsulphanyl group or a benzyloxy group,

and also with the proviso that the compounds of formula (I) are other than the following compounds :

- (1-benzylcyclopropyl)methanamine,
- 2-(benzyl)cyclopropanamine,
- 2-(phenoxycyclopropyl)methanamine,
- 2-(phenoxymethyl)-cyclopropanamine,
- (N,N-dimethyl)-2-(phenylsulphanyl)cyclopropanamine,
- (N,N-dimethyl)-2-(acetoxymethyl)-cyclopropanemethanamine,
- N,N-dimethyl-2-phenoxycyclopropanamine,

- 1-aminocyclopropyl carbonate.

An aryl group denotes a phenyl, biphenyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, indanyl or indenyl group, each of those groups being optionally substituted by one or more identical or different groups selected from halogen atoms, linear or branched (C_1-C_6)alkyl, hydroxy, cyano, nitro, linear or branched (C_1-C_6)alkoxy, linear or branched (C_2-C_7)acyl, linear or branched (C_1-C_6)alkoxycarbonyl, linear or branched (C_1-C_6)trihaloalkyl and linear or branched (C_1-C_6)trihaloalkoxy groups and amino groups (optionally substituted by one or two linear or branched (C_1-C_6)alkyl groups).

A heteroaryl group denotes a 5- to 12-membered, monocyclic aromatic or bicyclic system containing from one to three identical or different hetero atoms selected from oxygen, nitrogen and sulphur, one of the rings of which, in the case of a bicyclic system, is aromatic in character, and the other ring of which may be aromatic or partially hydrogenated, each of those groups being optionally substituted by one or more identical or different groups selected from the substituents defined hereinbefore for an aryl group.

In general, the 1,1-disubstituted and 1,2-disubstituted compounds relate to compounds having a moiety  and  , respectively.

Among the pharmaceutically acceptable acids there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphonic acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, camphoric acid etc..

Among the pharmaceutically acceptable bases there may be mentioned, without implying any limitation, sodium hydroxide, potassium hydroxide, triethylamine, tert-butylamine etc..

Preferred compounds of the invention are those compounds wherein n is an integer of from 0 to 2 inclusive.

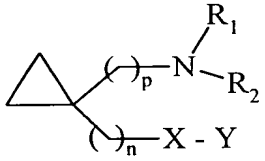
Advantageously, preferred compounds of the invention are those compounds wherein p is an integer having the value 0 or 1.

The substituents R_1 and R_2 that are preferred according to the invention are a hydrogen atom and a linear or branched $(C_1\text{-}C_6)$alkyl group.

The substituent X that is preferred according to the invention is an oxygen atom.

The substituents Y that are preferred according to the invention are groups selected from $-C(O)NR_3R_4$ wherein R_3 and R_4 are as defined for formula (I), acetyl, -C(O)-heteroaryl, aryl-$(C_1\text{-}C_6)$alkyl in which the alkyl moiety is linear or branched, and heteroaryl. Advantageously, the preferred heteroaryl group in the definitions of Y is a pyridyl group.

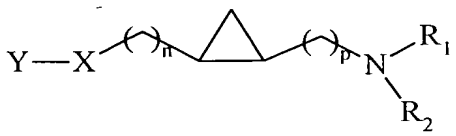
According to an advantageous embodiment of the invention, preferred compounds are 1,1-disubstituted compounds of formula (I) corresponding to formula **(IA)** :



(IA),

wherein n, p, X, Y, R_1 and R_2 are as defined for formula (I).

According to another advantageous embodiment of the invention, preferred compounds are 1,2-disubstituted compounds of formula (I) corresponding to formula **(IB)** :



(IB),

wherein n, p, X, Y, R_1 and R_2 are as defined for formula (I).

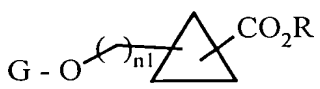
In especially advantageous manner, preferred compounds of the invention are :

- 2-[1-(dimethylamino)cyclopropyl]ethyl methylcarbamate,
- 2-[1-(dimethylamino)cyclopropyl]ethyl dimethylcarbamate,

- [1-(dimethylamino)cyclopropyl]methyl dimethylcarbamate,
- [1-(dimethylamino)cyclopropyl]methyl acetate,
- 2-[1-(dimethylamino)cyclopropyl]ethyl acetate,
- 1-[(dimethylamino)methyl]cyclopropyl acetate,
- [1-(dimethylamino)cyclopropyl]methyl nicotinate,
- *N*,*N*-dimethyl-1-[(3-pyridyloxy)methyl]cyclopropanamine,
- *N*-methyl-1-[(3-pyridyloxy)methyl]cyclopropanamine,
- *N*,*N*-dimethyl-1-[(3-pyridylmethoxy)methyl]cyclopropanamine,
- *N*,*N*-dimethyl-1-[2-(3-pyridyloxy)ethyl]cyclopropanamine,
- 4-({2-[1-dimethylamino)cyclopropyl]ethyl}sulphanyl)phenol,
- (±)-*cis*-2-(dimethylamino)cyclopropyl methylcarbamate,
- (±)-*trans*-2-(dimethylamino)cyclopropyl methylcarbamate,
- (±)-*cis*-2-(dimethylamino)cyclopropyl acetate,
- (±)-*trans*-2-(dimethylamino)cyclopropyl acetate,
- (±)-*cis*-2-(dimethylamino)cyclopropyl]methyl acetate,
- (±)-*trans*-2-(dimethylamino)cyclopropyl]methyl acetate,
- (±)-*cis*-2-[(benzyloxy)methyl]-*N*,*N*-dimethylcyclopropanamine,
- (±)-*trans*-2-[(benzyloxy)methyl]-*N*,*N*-dimethylcyclopropanamine, and
- (±)-*trans*-2-[(dimethylamino)methyl]cyclopropyl acetate.

The isomers, as well as the addition salts with a pharmaceutically acceptable acid or base, of the preferred compounds form an integral part of the invention.

The present invention relates also to a process for the preparation of compounds of formula (I), which process is characterised in that there is used as starting material a compound of formula **(II)** :

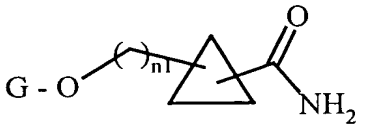


(II),

wherein G represents a protecting group conventionally used in organic synthesis, R represents a hydrogen atom or a linear or branched (C_1-C_6)alkyl group, and n_1 represents 0 or 1,

which compounds of formula (II) are :

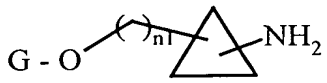
✶ ***either*** reacted with liquid ammonia in the presence of an alkali metal cyanide in an alcoholic solvent to yield the compounds of formula **(III)** :



(III),

wherein G represents a protecting group for hydroxy functions and n_1 represents 0 or 1,

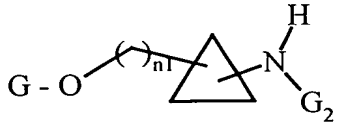
which compounds of formula (III) are treated with a dihalide in the presence of a base such as sodium hydroxide to yield the compounds of formula **(IV)** :



(IV),

wherein G and n_1 are as defined hereinbefore,

the primary amine function of which compounds of formula (IV) is selectively protected by a protecting group G_2 customarily used in organic chemistry such as the group BOC (t-butoxycarbonyl) to yield the compounds of formula **(V)** :



(V),

wherein n_1, G and G_2 are as defined hereinbefore,

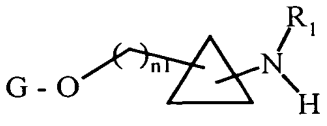
which compounds of formula (V) are then successively :

- treated, in a basic medium, with a compound of formula **(VIA)** :

$$R_1 - L_1 \qquad \textbf{(VIA),}$$

wherein R_1 is as defined for formula (I) and L_1 represents a customary leaving group of organic synthesis,

- the amine function of which is then deprotected, which compounds either undergo no further treatment and consequently yield compounds of formula **(VIIA)** :



(VIIA),

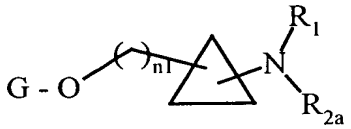
wherein R_1, n_1 and G are as defined hereinbefore,

or are reacted with a compound of formula **(VIB)** :

$$R_{2a} - L_1 \qquad \textbf{(VIB)},$$

wherein R_{2a} has the same meanings as R_2 as defined for formula (I) except for the meaning of a hydrogen atom and L_1 is as defined hereinbefore,

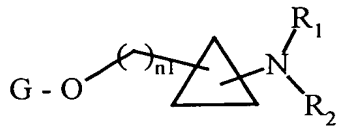
to yield compounds of formula **(VIIB)** :



(VIIB),

wherein R_1, R_{2a}, n_1 and G are as defined hereinbefore,

the totality of the compounds of formulae (VIIA) and (VIIB) forming the compounds of formula **(VII)** :



(VII),

wherein n_1, G, R_1 and R_2 are as defined hereinbefore,

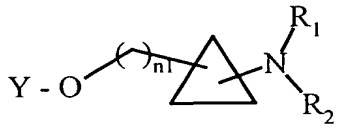
the hydroxy function of which compounds of formula (VII) is deprotected, which compounds are then :

- **<u>either</u>** treated with a compound of formula **(VIII)** :

$$Y - L_1 \qquad \textbf{(VIII)},$$

wherein Y is as defined for formula (I) and L_1 is as defined hereinbefore,

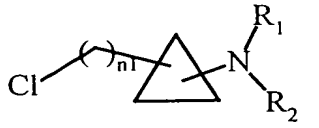
to yield compounds of formula **(I/a)**, a particular case of the compounds of formula (I) :



(I/a),

wherein n_1, Y, R_1 and R_2 are as defined for formula (I),

- **<u>or</u>** reacted with $SOCl_2$ to yield compounds of formula **(IX)** :



(IX),

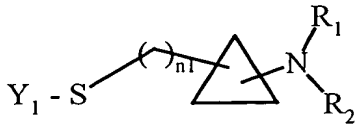
wherein n_1, R_1 and R_2 are as defined hereinbefore,

which compounds of formula (IX) are reacted, in a basic medium, with a compound of formula **(X)** :

$$Y_1 - SH \qquad \textbf{(X)},$$

wherein Y_1 represents an aryl group, an aryl-(C_1-C_6)alkyl group in which the alkyl moiety is linear or branched, a heteroaryl group or a heteroaryl-(C_1-C_6)alkyl group in which the alkyl moiety is linear or branched,

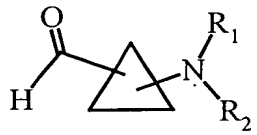
to yield compounds of formula **(I/b)**, a particular case of the compounds of formula (I) :



(I/b),

wherein Y_1, n_1, R_1 and R_2 are as defined hereinbefore,

♦ <u>or</u>, when n_1 has the value 1, subjected to the action of a conventional oxidising agent of organic synthesis to yield compounds of formula **(XI)** :



(XI),

wherein R_1 and R_2 are as defined hereinbefore,

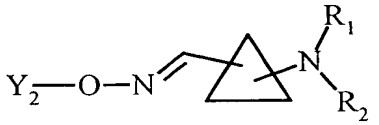
which compounds of formula (XI) are :

↳ *<u>either</u>* treated with a hydroxylamine of formula **(XII)** :

$$H_2N - OY_2 \qquad \textbf{(XII)},$$

wherein Y_2 represents a hydrogen atom or a group Y_1 as defined hereinbefore,

to yield compounds of formula **(I/c)**, a particular case of the compounds of formula (I) :



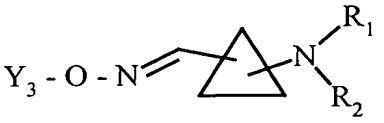
(I/c),

wherein Y_2, R_1 and R_2 are as defined hereinbefore,

which compounds of formula (I/c), in the particular case where Y_2 represents a hydrogen atom, are subjected to the action of a compound of formula **(XIV)** :

$$Y_3 - L_1 \qquad \textbf{(XIV)},$$

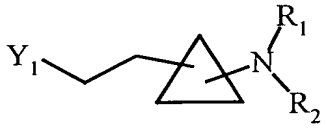
wherein L_1 is as defined hereinbefore and Y_3 represents a group of formula -C(O)-A or -C(S)-A as defined for formula (I), to yield compounds of formula **(I/d)**, a particular case of the compounds of formula (I) :



(I/d),

wherein Y_3, R_1 and R_2 are as defined hereinbefore,

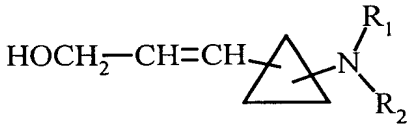
↳ *or* treated under Wittig reaction conditions and then subjected to the action of a customary reducing agent of organic synthesis to yield compounds of formula **(I/e)**, a particular case of the compounds of formula (I),



(I/e),

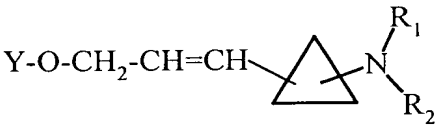
wherein Y_1, R_1 and R_2 are as defined hereinbefore,

↳ *or* subjected to the action of a compound of formula $Ph_3P=CH-CO_2Et$ and then reduced by the action of a reducing agent of organic synthesis to yield compounds of formula **(XV)** :



(XV),

wherein R_1 and R_2 are as defined hereinbefore,
which compounds of formula (XV) are treated with a compound of formula (VIII) as defined hereinbefore to yield compounds of formula **(I/f)**, a particular case of the compounds of formula (I) :



(I/f),

wherein Y, R_1 and R_2 are as defined for formula (I),

♦ <u>or</u>, when n_1 has the value 1, converted into their corresponding halogenated derivative under customary conditions of organic chemistry and then reacted with an alkali metal cyanide in the presence of dimethyl sulphoxide to yield compounds of formula **(XVI)** :

(XVI),

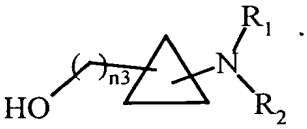
wherein R_1 and R_2 are as defined hereinbefore,

which compounds of formula (XVI) are converted into an ester under conventional conditions and then subjected to a reducing agent to yield compounds of formula **(XVIIA)** :

(XVIIA),

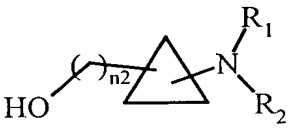
wherein R_1 and R_2 are as defined hereinbefore,

which compounds of formula (XVIIA) may be subjected again to the same series of reactions that yielded the compounds of formulae (XVI) and (XVII) to yield compounds of formula **(XVIIB)** :



(XVIIB),

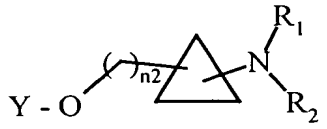
wherein R_1 and R_2 are as defined hereinbefore and n_3 is an integer of from 3 to 6 inclusive, the totality of the compounds of formulae (XVIIA) and (XVIIB) forming the compounds of formula **(XVIII)** :



(XVIII),

wherein R_1 and R_2 are as defined hereinbefore and n_2 is an integer of from 2 to 6 inclusive,

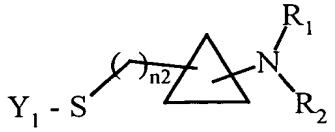
↳ *<u>either</u>* reacted with a compound of formula $Y\text{-}L_1$ as described hereinbefore to yield compounds of formula **(I/g)**, a particular case of the compounds of formula (I) :



(I/g),

wherein Y, n_2, R_1 and R_2 are as defined hereinbefore,

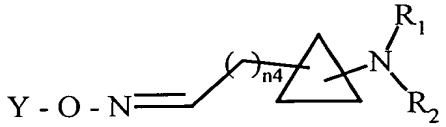
↳ *or* reacted with $SOCl_2$ and then treated with a compound of formula (X) as described hereinbefore to yield compounds of formula **(I/h)**, a particular case of the compounds of formula (I),



(I/h),

wherein Y_1, n_2, R_1 and R_2 are as defined hereinbefore,

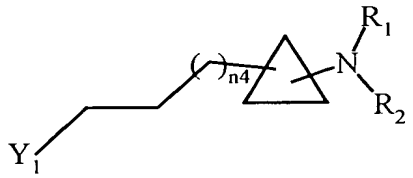
↳ *or* subjected to the action of an oxidising agent, the aldehyde intermediate obtained then being reacted with a hydroxylamine of formula (XII) as described hereinbefore and wherein Y_2 specifically represents a hydrogen atom and then, if desired, the compounds obtained are subjected to the action of a compound of formula (XIV) as described hereinbefore to yield compounds of formula **(I/i)**, a particular case of the compounds of formula (I) :



(I/i),

wherein R_1, R_2 and Y are as defined for formula (I) and n_4 represents an integer having a value of (n_2-1) wherein n_2 is as defined hereinbefore,

↳ *or* treated, after the action of an oxidising agent, under Wittig reaction conditions and then treated under conventional reduction conditions of organic synthesis to yield compounds of formula **(I/j)**, a particular case of the compounds of formula (I) :



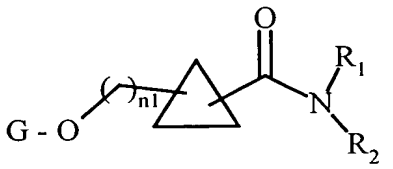
(I/j),

wherein Y_1, n_4, R_1 and R_2 are as described hereinbefore,

✶ ***or*** reacted in the presence of Me_3Al in a non-polar solvent with a compound of formula **(XIX)** :

HNR_1R_2 **(XIX),**

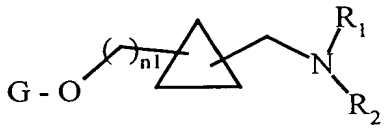
wherein R_1 and R_2 are as defined for formula (I), to yield compounds of formula **(XX)** :



(XX),

wherein n_1, G, R_1 and R_2 are as defined hereinbefore,

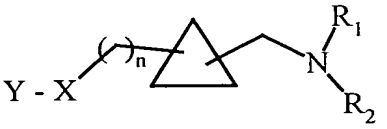
which compounds of formula (XX) are subjected to the action of a reducing agent conventionally used in organic synthesis, to yield the compounds of formula **(XXI)** :



(XXI),

wherein G, n_1, R_1 and R_2 are as defined hereinbefore,

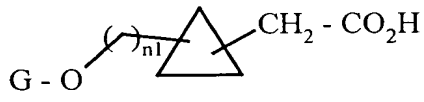
which compounds of formula (XXI) may be subjected to the totality of reactions to which the compounds of formula (VII) are subjected, to yield compounds of formula **(I/k)**, a particular case of the compounds of formula (I) :



(I/k),

wherein X, Y, n, R_1 and R_2 are as defined for formula (I),

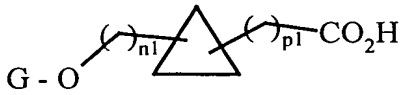
✶ ***or*** reacted with thionyl chloride, when R represents a hydrogen atom, and then placed in the presence of diazomethane in an aqueous medium to yield compounds of formula **(XXII)** :



(XXII),

wherein n_1 and G are as defined hereinbefore,

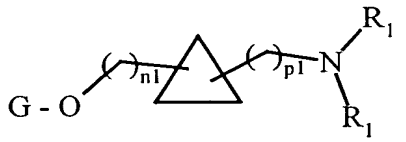
which compounds of formula (XXII) may again be subjected several times to the same reaction series to yield compounds of formula **(XXIII)** :



(XXIII),

wherein n_1 and G are as defined hereinbefore and p_1 represents an integer of from 2 to 6 inclusive,

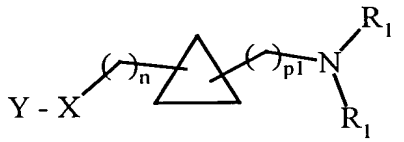
which compounds of formula (XXIII) are reacted with diphenylphosphoryl azide, hydrolysed and then treated with a compound of formula (VIA) as described hereinbefore to yield compounds of formula **(XXIV)** :



(XXIV),

wherein R_1 is as defined for formula (I) and G, n_1 and p_1 are as defined hereinbefore,

which compounds of formula (XXIV) may be subjected to the totality of reactions to which the compounds of formula (VII) are subjected, to yield compounds of formula **(I/l)**, a particular case of the compounds of formula (I) :

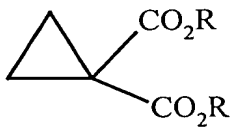


(I/l),

wherein X, Y, R_1 and n are as defined for formula (I) and p_1 is as defined hereinbefore,

the totality of compounds of formulae (I/a) to (I/l) constituting the totality of the compounds of the invention, which are purified, where appropriate, according to a conventional purification technique, which may be separated into their different isomers according to a conventional separation technique, and which are converted, where appropriate, into addition salts thereof with a pharmaceutically acceptable acid or base.

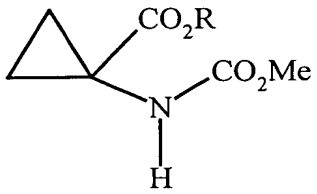
According to an embodiment of the preparation process, certain compounds of the invention of formula (IA) may be obtained starting from compounds of formula **(a_1)** :



(a_1),

wherein R represents a linear or branched (C_1-C_6)alkyl group,

one of the ester functions of which compounds of formula (a_1) is hydrolysed, which compounds are then subjected to the action of diphenylphosphoryl azide and methanol, in a polar and aprotic medium, to yield compounds of formula **(b_1)** :



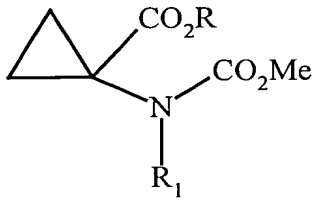
(b_1),

wherein R is as defined hereinbefore,

the carbamate function of which compounds of formula (b_1) is substituted by the action of a compound of formula **(c_1)** :

R_1 - Hal **(c_1),**

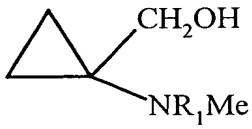
wherein R_1 is as defined for formula (I) and Hal represents a halogen atom, to yield compounds of formula **(d_1)** :



(d_1),

wherein R and R_1 are as defined hereinbefore,

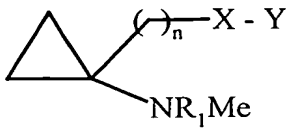
which compounds of formula (d_1) are reduced to yield compounds of formula **(e_1)** :



(e_1),

wherein R_1 is as defined hereinbefore,

which compounds of formula (e_1) may be subjected to any of the reactions to which the compounds of formula (VII) are subjected in the general procedure for the formation of compounds of formula (I), to yield compounds of formula **(I/m)**, a particular case of the compounds of formula (I) :

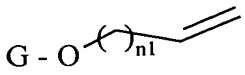


(I/m),

wherein R_1, n, X and Y are as defined for formula (I).

The compounds of formulae (II), (VIA), (VIB), (VIII), (X), (XII), (XIV), (XVIII), (a_1) and (c_1) are either commercial products or are obtained according to conventional methods of organic synthesis well known to the person skilled in the art.

1,2-Disubstituted compounds of formula (II) may especially be obtained starting from hydroxyallyl or hydroxyvinyl compounds wherein the hydroxy function is protected by a conventional protecting group of organic synthesis. These compounds of formula **(II/a)** :



(II/a),

wherein G is a protecting group and n_1 represents 0 or 1, are reacted, in the presence of rhodium tetraacetate, with a compound of formula $N_2CH_2CO_2R$, wherein R represents a linear or branched (C_1-C_6)alkyl group, to yield compounds of formula **(II)** as expected :

(II).

With respect to the conventional methods for protecting and deprotecting hydroxy or amino functions, the person skilled in the art will easily refer to the book of T. W. Greene, "Protective Group in Organic Synthesis", Willey-Interscience, New York, 1981.

Generally, isomers of the compounds of the invention are understood to be optical isomers such as enantiomers and diastereoisomers. More especially, pure enantiomeric forms of the compounds of the invention may be separated by starting from mixtures of enantiomers which are reacted with a racemate-separating agent that can be released, the said agent being itself in the form a pure enantiomer, which allows the corresponding diastereoisomers to be obtained. The diastereoisomers are then separated according to the separation techniques well known to the person skilled in the art, such as crystallisation or

chromatography, and the separating agent is then removed using conventional techniques of organic synthesis, resulting in a pure enantiomer being obtained.

The compounds of the invention that are present in the form of a mixture of diastereoisomers are isolated in a pure form by using conventional separation techniques such as chromatography.

In certain particular cases, the process for the preparation of compounds of the invention may result in the predominant formation of one enantiomer or diastereoisomer over the other.

By virtue of their pharmacological properties as nicotinic ligands, and their selectivity for the receptor sub-type $\alpha 4\beta 2$, the compounds of the present invention are of use, as medicaments, in the treatment of deficiencies of memory associated with cerebral ageing and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease and frontal lobe and subcortical dementias, and also for the treatment of mood disorders, Tourette's syndrome, attention-deficit hyperactivity syndrome, tobacco withdrawal and pain.

The present invention relates also to pharmaceutical compositions comprising as active ingredient at least one compound of formula (I), an isomer thereof, or an addition salt thereof with a pharmaceutically acceptable acid or base, alone or in combination with one or more pharmaceutically acceptable, inert, non-toxic excipients or carriers.

Among the pharmaceutical compositions according to the invention, there may be mentioned more especially those that are suitable for oral, parenteral (intravenous, intramuscular or subcutaneous), per- or trans-cutaneous, intravaginal, rectal, nasal, perlingual, buccal, ocular or respiratory administration.

Pharmaceutical compositions according to the invention for parenteral injections especially include aqueous and non-aqueous sterile solutions, dispersions, suspensions and emulsions, and also sterile powders for reconstituting injectable solutions or dispersions.

Pharmaceutical compositions according to the invention for oral administration in solid form especially include tablets or dragées, sublingual tablets, sachets, gelatin capsules and granules and, for oral, nasal, buccal or ocular administration in liquid form, especially include emulsions, solutions, suspensions, drops, syrups and aerosols.

Pharmaceutical compositions for rectal or vaginal administration are preferably suppositories, and those for per- or trans-cutaneous administration especially include powders, aerosols, creams, ointments, gels and patches.

The pharmaceutical compositions mentioned hereinbefore illustrate the invention but do not limit it in any way.

Among the pharmaceutically acceptable, inert, non-toxic excipients or carriers there may be mentioned, by way of non-limiting example, diluents, solvents, preservatives, wetting agents, emulsifiers, dispersing agents, binders, swelling agents, disintegrating agents, retardants, lubricants, absorbents, suspending agents, colourants, aromatising agents etc..

The useful dosage varies according to the age and weight of the patient, the administration route, the pharmaceutical composition used, the nature and severity of the disorder and the administration of any associated treatments. The dosage ranges from 1 mg to 500 mg per day in one or more administrations.

The Examples that follow illustrate the invention but do not limit it in any way.

The starting materials used are products that are known or that are prepared according to known operating procedures. The various Preparations yield synthesis intermediates that are useful in preparation of the compounds of the invention.

The structures of the compounds described in the Examples and Preparations were determined according to the usual spectrophotometric techniques (infrared, nuclear magnetic resonance, mass spectrometry, ...).

The melting points were determined using either a Kofler hot-plate or a hot-plate under a microscope. When the compound is in the form of a salt, the melting point given and the elemental microanalysis refer to the salt form of the compound.

PREPARATION A : (±)-*cis*-2-(Dimethylamino)cyclopropanol hydrochloride

***Step 1* : 2-(Vinyloxy)tetrahydro-2*H*-pyran**

A mixture of 1.52 mol of 2-(2-chloroethoxy)-tetrahydro-2*H*-pyran, 93 g of sodium hydroxide reduced to a powder and 25 g of tetrabutylammonium monosulphate is stirred for 1 hour and then distilled at 50°C and 20 torr. The distillate is then dried over sodium sulphate, allowing the expected product to be isolated.

***Step 2* : Ethyl 2-(tetrahydro-2*H*-pyran-2-yloxy)cyclopropanecarboxylate**

To a solution of 0.75 mol of the compound obtained in Step 1 in 200 ml of ether there are added 1.5 g of rhodium acetate and then, over 6 hours, a solution of 93 g of ethyl diazoacetate in 50 ml of ether. After stirring at ambient temperature for 16 hours, the reaction mixture is filtered and is then distilled at 50-90°C and 0.5 torr. The residue obtained is redistilled at 80-84°C and 0.2 torr, allowing the expected product to be isolated.

***Step 3* : 2-(Tetrahydro-2*H*-pyran-2-yloxy)cyclopropanecarboxamide**

In an autoclave, a solution of 0.25 mol of the compound obtained in Step 2, 2 g of sodium cyanide, 300 ml of a 2N solution of ammonia in methanol and 80 ml of liquid ammonia is heated at 65°C for 5 days and is then concentrated to dryness. The residue is taken up in a mixture of dichloromethane/saturated potassium carbonate solution, filtered over Celite and then treated in conventional manner. After evaporating under reduced pressure, the residue is triturated in petroleum ether, filtered, rinsed and dried, allowing the expected product to be isolated.

Step 4 **: 2-(Tetrahydro-2*H*-pyran-2-yloxy)cyclopropylamine**

To a cooled solution of 2.2 mol of sodium hydroxide in 800 ml of water there are added 33 g of chlorine and then 52 g of the compound obtained in Step 3. After returning to ambient temperature, the reaction mixture is heated at 65°C for 16 hours, then cooled to 20°C and saturated with potassium carbonate. After extracting with ether, the combined organic phases are dried and then concentrated under reduced pressure, allowing the expected product to be isolated.

Step 5 **: *tert*-Butyl 2-(tetrahydro-2*H*-pyran-2-yloxy)cyclopropylcarbamate**

0.65 mol of triethylamine is added to a solution of 0.25 mol of the compound obtained in Step 4 in 300 ml of dichloromethane. The mixture is cooled to 0°C and 0.3 mol of di-*tert*-butyl dicarbonate in 250 ml of dichloromethane is added over one hour. After returning to ambient temperature, the reaction mixture is stirred for 20 hours and then 200 ml of a saturated sodium carbonate solution are added. After separation, the organic phases are treated in customary manner and then concentrated under reduced pressure. Chromatography of the residue over silica gel (dichloromethane/ethyl acetate : 95/5) allows the expected product to be isolated in the form of a diastereoisomeric mixture.

Step 6 **: *cis-tert*-Butyl *N*-methyl-[2-(tetrahydro-2*H*-pyran-2-yloxy)cyclopropyl]-carbamate and *trans-tert*-butyl *N*-methyl-[2-tetrahydro-2*H*-pyran-2-yloxy)cyclopropyl]carbamate**

26 g of the compound obtained in Step 5 in 20 ml of dimethylformamide are added to a solution, cooled to 0°C, of 4.4 g of sodium hydride in 250 ml of dimethylformamide. After returning to ambient temperature, the mixture is stirred for 2 hours and then 15.6 g of methyl iodide are added over 15 minutes. After stirring for 16 hours, the reaction mixture is concentrated and taken up in a mixture of ether/saturated sodium carbonate solution. The organic phases are then treated in customary manner and subsequently concentrated. Chromatography over silica gel (cyclohexane/tetrahydrofuran) allows the *trans* isomer and then the *cis* isomer of the expected product to be isolated.

Step 7 : *cis*-*N*,*N*-Dimethyl-2-(tetrahydro-2*H*-pyran-2-yloxy)cyclopropanamine

46 ml of Red-Al®, 65 % in toluene, are added to a solution, cooled to 0°C, of 7.5 g of the *cis* isomer obtained in the previous Step in 75 ml of tetrahydrofuran. The reaction mixture is stirred at 0°C for 2 hours and at ambient temperature for 16 hours and is then cooled to 0°C and hydrolysed with 100 ml of distilled water. After extracting with ether, the combined organic phases are treated in customary manner and then concentrated. Chromatography of the residue over silica gel (dichloromethane/tetrahydrofuran : 90/10) allows the expected product to be isolated.

Step 8 : (±)-*cis*-2-(Dimethylamino)cyclopropanol hydrochloride

6 ml of a 4N solution of hydrochloric acid in dioxane are added, under an inert atmosphere, to 1.8 g of the compound obtained in Step 7 in 30 ml of ether. After 16 hours at ambient temperature, the mixture is filtered, rinsed with ether and then dried under reduced pressure, allowing the expected product to be isolated.

Melting point : 160-162°C

PREPARATION B : (±)-*trans*-2-(Dimethylamino)cyclopropanol hydrochloride

Step 1 : *trans*-*N*,*N*-Dimethyl-2-(tetrahydro-2*H*-pyran-2-yloxy)-cyclopropanamine

The product is obtained according to the procedure of Step 7 of Preparation A using as substrate the *trans* isomer obtained in Step 6 of Preparation A.

Step 2 : (±)-*trans*-2-(Dimethylamino)cyclopropanol hydrochloride

The product is obtained according to the procedure of Step 8 of Preparation A using as substrate the compound obtained in Step 1. The product recrystallises from acetonitrile.

Melting point : 118-120°C

PREPARATION C : (±)-*trans*-Methyl 2-[(benzyloxy)methyl]cyclopropyl (methyl)carbamate

Step 1 : Ethyl 2-[(benzyloxy)methyl]cyclopropanecarboxylate

31.2 g of ethyl diazoacetate are added to a solution of 0.3 mol of allyl benzyl ether in 150 ml of ether with the aid of a push-syringe. After stirring for 16 hours, 31.2 g of ethyl diazoacetate are added again. After 24 hours the mixture is filtered. The organic phase is washed with saturated $NaHCO_3$ solution and then treated in customary manner. Chromatography over silica gel (dichloromethane) allows the expected product to be obtained.

Step 2 : 2-[(Benzyloxy)methyl]cyclopropanecarboxylic acid

A solution of 0.23 mol of the compound obtained in Step 1 in 500 ml of ethanol, 230 ml of 1N sodium hydroxide solution and 5 ml of dimethyl sulphoxide is heated at reflux for 2 hours and is then concentrated. The residue is taken up in a mixture of water/ether. After conventional treatment, the combined organic phases are concentrated. Chromatography of the residue over silica gel (dichloromethane/tetrahydrofuran : 97/3) allows a *cis/trans* mixture of the products obtained to be isolated, some of the fractions of which have a preponderance of the *cis* isomer and some a preponderance of the *trans* isomer.

Step 3 : (±)-*trans*-Methyl 2-[(benzyloxy)methyl]cyclopropylcarbamate

14.7 g of diphenylphosphoryl azide are added to 11 g of the *trans* isomer of the product obtained in Step 2 in 100 ml of toluene, and 5.4 g of triethylamine. The mixture is heated at 80°C for 2 hours 30 minutes, and then 2.6 g of methanol are added. After 16 hours at 80°C, the reaction mixture is cooled, washed with saturated $NaHCO_3$ solution, dried and then concentrated. Chromatography of the residue over silica gel (dichloromethane) allows the expected product to be isolated in a *trans/cis* diastereoisomeric ratio of : 94/6.

Step 4 : (±)-*trans*-Methyl 2-[(benzyloxy)methyl]cyclopropyl(methyl)carbamate

2.1 g of sodium hydride are added, in fractions, to a solution, cooled to 0°C, of 10.2 g of the compound obtained in Step 3 in 150 ml of dimethylformamide. After 30 minutes at 0°C, and then 24 hours at ambient temperature, 7.24 g of methyl iodide are added and stirring is carried out for 72 hours. After evaporating off the solvent, the residue is taken up in ether and washed with saturated $NaHCO_3$ solution and then with 10 % lithium chloride solution. After customary treatment, chromatography of the residue over silica gel (dichloromethane) allows the expected product to be isolated.

PREPARATION D : (±)-*cis*-Methyl 2-[(benzyloxy)methyl]cyclopropyl-(methyl)carbamate

Step 1 : (±)-*cis*-Methyl 2-[(benzyloxy)methyl]cyclopropylcarbamate

The product is obtained according to the procedure of Step 3 of Preparation C using as substrate the *cis* isomer obtained in Step 2 of Preparation C. The product is isolated in a *cis/trans* diastereoisomeric ratio of : 77/23.

Step 2 : (±)-*cis*-Methyl 2-[(benzyloxy)methyl]cyclopropyl(methyl)carbamate

The product is obtained according to the procedure of Step 4 of Preparation C using as substrate the product obtained in Step 1.

PREPARATION E : *trans*-2-[(Dimethylamino)methyl]cyclopropanol hydrochloride

Step 1 : *N,N*-Dimethyl-2-(tetrahydro-2*H*-pyran-2-yloxy)cyclopropane-carboxamide

6.1 g of dimethylamine are added, at -15°C, to 70 ml of a 2M solution of trimethyl-aluminium in toluene, and 250 ml of toluene. After 20 minutes, the mixture is brought to

Step 2 of Preparation A in 75 ml of toluene are added. The reaction mixture is then heated at 85°C for 16 hours and is then cooled in an ice bath; 270 ml of 0.5N hydrochloric acid solution are added and the mixture is filtered and separated. The combined organic phases are treated in customary manner and then concentrated under reduced pressure, allowing the expected product to be obtained in a *trans/cis* diastereoisomeric ratio of 80/20.

Step 2 : *trans*-*N*,*N*-Dimethyl-*N*-{[2-(tetrahydro-2*H*-pyran-2-yloxy)-cyclopropyl]methyl}amine

14 g of the compound obtained in Step 1 in 50 ml of ether are slowly added to a suspension of 3.1 g of $AlLiH_4$ in 120 ml of ether. After 16 hours at reflux, the reaction mixture is cooled to 0°C, hydrolysed, filtered and then concentrated under reduced pressure. Chromatography of the residue over silica gel (dichloromethane/methanol : 90/10) allows the expected product to be isolated in a *trans/cis* diastereoisomeric ratio of 99/1.

Step 3 : *trans*-2-[(Dimethylamino)methyl]cyclopropanol hydrochloride

The product is obtained according to the procedure of Step 8 of Preparation A using as substrate the compound obtained in Step 2 and adding ethanol to the reaction mixture.
Melting point : 93-96°C

PREPARATION F : [1-(Dimethylamino)cyclopropyl]methanol

Step 1 : 1-(Methoxycarbonyl)cyclopropanecarboxylic acid

1.45 litres of 1N sodium hydroxide solution are added to a solution, cooled to 5°C, of 1.45 mol of dimethyl 1,1-cyclopropanedicarboxylate in 2.5 litres of methanol. After stirring for 4 days at ambient temperature, the mixture is three-quarters concentrated, extracted with ether and then treated in customary manner, allowing the expected product to be isolated.

Step 2 : Methyl 1-[(methoxycarbonyl)amino]cyclopropanecarboxylate

300 g of diphenylphosphoryl azide are added to a solution, heated to 80°C, of 1.09 mol of the compound obtained in Step 1 in 1.09 litres of toluene and 153 ml of triethylamine. The reaction is markedly exothermic. When all evolution of gas has ceased, the reaction mixture is cooled to 50°C, 66.3 ml of methanol are added, and the mixture is again heated at 70°C for 2 hours. After cooling and conventional treatment, chromatography over silica gel (dichloromethane/methanol : 97/3) allows the expected product to be isolated.

Step 3 : Methyl 1-[(methoxycarbonyl)(methyl)amino]cyclopropane-carboxylate

24.7 g of sodium hydride are added, in fractions, to a solution, cooled to 5°C, of 99.7 g of the compound obtained in Step 2 in 1.7 litres of anhydrous dimethylformamide. After 15 minutes at 5°C and then 3 hours at ambient temperature, 38.2 ml of methyl iodide are added dropwise. After reacting for 20 hours, the mixture is evaporated. The residue is taken up in ether and then treated in conventional manner. Chromatography over silica gel (dichloromethane) allows the expected product to be isolated.

Step 4 : [1-(Dimethylamino)cyclopropyl]methanol

44 g of the compound obtained in Step 3 dissolved in 350 ml of tetrahydrofuran are added, over 30 minutes, to a solution of 44 g of $LiAlH_4$ in 1.05 litres of tetrahydrofuran. After refluxing for 20 hours, the mixture is cooled to 5°C, and 44 ml of water, 44 ml of 4N sodium hydroxide solution and then 132 ml of water are added. Filtration, followed by concentration under reduced pressure, allows the expected product to be isolated.

Melting point : < 50°C

PREPARATION G : 1-[(Dimethylamino)methyl]cyclopropanol hydrochloride

Step 1 : 1-Hydroxy-*N*,*N*-dimethylcyclopropanecarboxamide

17.1 ml of trimethylsilyl chloride are added dropwise to a solution of 6 g of 1-hydroxy-cyclopropanecarboxylic acid in 120 ml of dichloromethane and 10.5 ml of pyridine. After stirring for 4 hours at ambient temperature, the mixture is cooled to 0°C, and 10 drops of dimethylformamide and then 5.4 ml of oxalyl chloride are added. The reaction mixture is stirred at 0°C for 1 hour and at ambient temperature for 1 hour; a solution of 2.4 g of dimethylamine in 10 ml of pyridine is then added. Stirring is continued for 20 hours and then, after cooling to 0°C, 14 g of citric acid in 120 ml of methanol are added. After returning to ambient temperature for one hour, the reaction mixture is washed with 1N hydrochloric acid solution and then with $NaHCO_3$-saturated solution and then NaCl-saturated solution. The organic phase is treated in conventional manner and chromatography over silica gel (dichloromethane/tetrahydrofuran : 90/10) allows the expected product to be isolated.

Step 2 : 1-[(Dimethylamino)methyl]cyclopropanol hydrochloride

1.5 g of the compound obtained in Step 1 in 20 ml of ether are added slowly to a solution of 0.9 g of $AlLiH_4$ in 30 ml of ether. After refluxing for 5 hours, the reaction mixture is cooled and hydrolysed with ice. The aqueous phase is separated off, saturated with potassium carbonate and extracted with dichloromethane. The organic phases are dried and then concentrated under reduced pressure. The residue is taken up in 25 ml of ether and 2 ml of a 4N solution of hydrochloric acid in dioxane. The precipitate is filtered off, allowing the expected product to be isolated.

PREPARATION H : 2-[1-(Dimethylamino)cyclopropyl]ethanol hydrochloride

Step 1 : 1-(Chloromethyl)-*N*,*N*-dimethylcyclopropanamine hydrochloride

80 ml of ethereal HCl are added to a solution of 18.4 g of the compound of Preparation F in 240 ml of ether. The precipitate obtained is filtered off, rinsed with ether, dried and then diluted with 320 ml of toluene to which there are added, dropwise, 32 ml of thionyl chloride. After 3 hours at 60°C, the mixture is cooled to 5°C, filtered, washed with toluene and dried, allowing the expected product to be isolated.

Melting point : 198°C

Step 2 : [1-(Dimethylamino)cyclopropyl]acetonitrile

30.3 g of the compound obtained in Step 1 are added to a solution of 43 g of sodium cyanide and 3.5 g of potassium iodide in 400 ml of dimethyl sulphoxide. After stirring for 20 hours at ambient temperature, 490 ml of 10 % aqueous sodium carbonate solution and then sodium chloride are added. The mixture is extracted with ether. After conventional treatment of the organic phases, chromatography over silica gel allows the expected product to be isolated.

Step 3 : Methyl [1-(dimethylamino)cyclopropyl]acetate

To a solution, cooled to 5°C, of 14.5 g of the compound obtained in Step 2 in 230 ml of anhydrous methanol there are added 40 ml of 2N anhydrous methanolic HCl and then gaseous HCl until saturated. The mixture is stirred at ambient temperature for 20 hours and then evaporated. The residue is taken up in sodium carbonate solution and is extracted with dichloromethane. After conventional treatment of the organic phases, chromatography over silica gel (dichloromethane/tetrahydrofuran : 95/5) allows the expected product to be isolated.

Step 4 : 2-[1-(Dimethylamino)cyclopropyl]ethanol hydrochloride

10.25 g of the compound obtained in Step 3 dissolved in 200 ml of tetrahydrofuran are slowly added to a solution of 5 g of $AlLiH_4$ in 300 ml of tetrahydrofuran. After refluxing for 2 hours, the reaction mixture is cooled to 5°C and 10.7 ml of water, 10.7 ml of 4N sodium hydroxide and then 32.1 ml of water are added. After filtering and concentrating under reduced pressure, chromatography over silica gel (dichloromethane/methanol : 95/5) allows the expected product to be isolated, which is converted into its hydrochloride form by the action of a solution of hydrochloric acid in dioxane.

PREPARATION I : *tert*-Butyl 1-(hydroxymethyl)cyclopropyl(methyl)carbamate

Step 1 : Methyl 1-[(*tert*-butoxycarbonyl)amino]cyclopropanecarboxylate

A solution of 80 g of dimethyl 1,1-cyclopropanedicarboxylate and 78 ml of triethylamine in 550 ml of toluene, to which 152 g of diphenylphosphoryl azide are added, is heated at 80°C. After the evolution of gas has ceased, the temperature is brought to 50°C and 61 g of *tert*-butanol are added. After reacting for 7 hours at 80°C, the mixture is concentrated. The residue is taken up in ether, washed with saturated Na_2CO_3 solution, then with 1N hydrochloric acid solution and then with $NaHCO_3$ solution. After drying and evaporation of the organic phase, the residue is taken up in 300 ml of cyclohexane and then concentrated to dryness. The residue obtained is triturated in pentane, filtered and then dried, allowing the expected product to be isolated.

Step 2 : Methyl 1-[(*tert*-butoxycarbonyl)(methyl)amino]cyclopropane-carboxylate

The product is obtained according to the procedure of Step 3 of Preparation F using as substrate the compound obtained in Step 1.

Step 3 : *tert*-Butyl 1-(hydroxymethyl)cyclopropyl(methyl)carbamate

100 ml of a 2M solution of lithium borohydride in tetrahydrofuran is added to a solution of 23 g of the compound obtained in Step 2 in 100 ml of tetrahydrofuran. After stirring for 20 hours at ambient temperature and then refluxing for 8 hours, the reaction mixture is cooled to 0°C, hydrolysed, diluted with ether, separated, dried and concentrated. Chromatography of the residue over silica gel (dichloromethane/tetrahydrofuran : 95/5) allows the expected product to be isolated.

PREPARATION J : 1-(2-Chloroethyl)-*N*,*N*-dimethylcyclopropanamine

The product is obtained according to the procedure of Step 1 of Preparation H using as substrate the compound of Preparation H.

EXAMPLE 1 : (±)-*cis*-2-(Dimethylamino)cyclopropyl acetate hydrochloride

A solution, under an inert atmosphere, of 0.28 g of the compound of Preparation A in 4 ml of acetic acid, to which 0.22 g of acetyl chloride is added, is stirred at ambient temperature for 16 hours and is then concentrated. The residue is taken up in 10 ml of dioxane and concentrated to dryness again. The operation is repeated until crystallisation occurs. The crystals obtained are diluted in 10 ml of ether, filtered off and dried, allowing the expected product to be isolated.

Melting point : amorphous

Elemental microanalysis :

	C	H	N	Hal
% calculated	**46.11**	**7.90**	**7.68**	**19.44**
% found	**46.01**	**7.70**	**7.48**	**19.63**

EXAMPLE 2 : (±)-*cis*-2-(Dimethylamino)cyclopropyl methylcarbamate hydrochloride

A solution of 0.4 g of the compound of Preparation A in 30 ml of acetonitrile and 0.25 g of methyl isocyanate is heated at 80°C for 8 hours, and then evaporated. The residue is taken

up in a mixture of water/ether, and saturated with potassium carbonate. The organic phase is treated in customary manner and the residue is chromatographed over silica gel (dichloromethane/methanol : 97/3). The compound obtained is converted into its hydrochloride form in customary manner. The product obtained crystallises from a mixture of 5 % acetonitrile in ether.

Melting point : 105-110°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	**41.65**	**7.89**	**13.88**	**17.56**
% found	**41.68**	**7.88**	**13.93**	**18.25**

EXAMPLE 3 : (±)-*trans*-2-(Dimethylamino)cyclopropyl acetate hydrochloride

The product is obtained according to the procedure of Example 1 using as substrate the compound of Preparation B.

Melting point : 148-150°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	**46.80**	**7.85**	**7.80**	**19.83**
% found	**46.67**	**7.82**	**7.50**	**19.97**

EXAMPLE 4 : (±)-*trans*-2-(Dimethylamino)cyclopropyl methylcarbamate hydrochloride

The product is obtained according to the procedure of Example 2 using as substrate the compound of Preparation B.

Melting point : 158-160°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	**42.60**	**7.81**	**14.19**	**17.96**
% found	**42.54**	**7.69**	**13.97**	**18.09**

EXAMPLE 5 : (±)-*trans*-2-[(Benzyloxy)methyl]-*N*,*N*-dimethylcyclopropanamine hydrochloride

A solution, cooled to 5°C, of 7 g of the compound of Preparation C in 140 ml of tetrahydrofuran, to which there are added 60 ml of Red-Al® 65 % solution in toluene, is stirred for 2 hours at 5°C and for 16 hours at ambient temperature and is then cooled to 0°C and hydrolysed. The solution is then diluted with ether, filtered and separated, and the organic phase is concentrated. The residue is converted into its hydrochloride form in conventional manner, allowing the expected product to be obtained.

Melting point : 118-120°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	**64.59**	**8.34**	**5.79**	**14.66**
% found	**64.14**	**8.46**	**5.78**	**14.54**

EXAMPLE 6 : (±)-*cis*-2-[(Benzyloxy)methyl]-*N*,*N*-dimethylcyclopropanamine hydrochloride

The product is obtained according to the procedure of Example 5 using as substrate the compound of Preparation D.

Melting point : 90-92°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	**64.59**	**8.34**	**5.79**	**14.66**
% found	**64.35**	**8.07**	**5.84**	**14.84**

EXAMPLE 7 : (±)-*trans*-[2-(Dimethylamino)cyclopropyl]methyl acetate hydrochloride

Step 1 : (±)-*trans*-[2-(Dimethylamino)cyclopropyl]methanol hydrochloride

1.2 g of sodium are added, in portions, to a solution of 4 g of the compound of Example 5 in 200 ml of condensed liquid ammonia. After 3 hours, 100 ml of ether and then 5 ml of ethanol are added. Stirring is carried out for 16 hours and the mixture is then concentrated and taken up in dichloromethane. The organic phase is treated in conventional manner and then evaporated. Chromatography over silica gel (dichloromethane/methanol : 90/10) allows the expected product to be isolated, which is converted into its hydrochloride form.

Melting point : 88-90°C

Step 2 : (±)-*trans*-[2-(Dimethylamino)cyclopropyl]methyl acetate hydrochloride

The product is obtained according to the procedure of Example 1 using as substrate the compound obtained in Step 1.

Melting point : 144-146°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	**49.61**	**8.33**	**7.23**	**18.31**
% found	**49.58**	**8.34**	**7.11**	**18.09**

EXAMPLE 8 : (±)-*cis*-[2-(Dimethylamino)cyclopropyl]methyl acetate hydrochloride

Step 1 : (±)-*cis*-[2-(Dimethylamino)cyclopropyl]methanol hydrochloride

The product is obtained according to the procedure of Step 1 of Example 7 using as substrate the compound of Example 6.

Melting point : 112-114°C

Step 2 : (±)-*cis*-[2-(Dimethylamino)cyclopropyl]methyl acetate hydrochloride

The product is obtained according to the procedure of Example 1 using as substrate the compound obtained in Step 1.

Melting point : 108-110°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	**49.61**	**8.33**	**7.23**	**18.31**
% found	**49.37**	**8.34**	**7.16**	**18.24**

EXAMPLE 9 : (±)-*trans*-2-[(Dimethylamino)methyl]cyclopropyl acetate hydrochloride

The product is obtained according to the procedure of Example 1 using as substrate the compound of Preparation E.

Melting point : 100-105°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	**49.61**	**8.33**	**7.23**	**18.31**
% found	**49.32**	**8.37**	**7.11**	**18.26**

EXAMPLE 10 : [1-(Dimethylamino)cyclopropyl]methyl acetate hydrochloride

The product is obtained according to the procedure of Example 1 using as substrate the compound of Preparation F.

Melting point : 100-102°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	**49.61**	**8.33**	**7.23**	**18.31**
% found	**49.27**	**8.37**	**7.16**	**18.28**

EXAMPLE 11 : [1-(Dimethylamino)cyclopropyl]methyl dimethylcarbamate hydrochloride

To a solution, under an inert atmosphere, of 2.1 g of the compound of Preparation F in 20 ml of pyridine there are added 1.95 g of dimethylcarbamoyl chloride and then, after 48 hours at ambient temperature, the same amount of reagent. The reaction mixture is heated at reflux for 3 hours and then evaporated. The residue is taken up in dioxane and then concentrated again, taken up in ether and washed with $NaHCO_3$ solution. The organic phase is extracted with 0.1N HCl solution, and the aqueous phase is made alkaline with sodium carbonate and then extracted with ether. The organic phases are treated in conventional manner and concentrated. Chromatography of the residue over silica gel (dichloromethane/tetrahydrofuran : 90/10) allows the expected product to be isolated, which is converted into its hydrochloride form.

Melting point : 166-168°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	**48.54**	**8.60**	**12.58**	**15.92**
% found	**48.55**	**8.53**	**12.22**	**15.61**

EXAMPLE 12 : 1-[(Dimethylamino)methyl]cyclopropyl acetate hydrochloride

The product is obtained according to the procedure of Example 1 using as substrate the compound of Preparation G.

Melting point : 166-170°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	**49.61**	**8.33**	**7.23**	**18.31**
% found	**49.52**	**8.46**	**7.21**	**18.88**

EXAMPLE 13 : 2-[1-(Dimethylamino)cyclopropyl]ethyl acetate hydrochloride

The product is obtained according to the procedure of Example 1 using as substrate the compound of Preparation H.

Melting point : 79-81°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	**51.16**	**8.78**	**6.63**	**16.78**
% found	**51.05**	**8.60**	**6.90**	**16.94**

EXAMPLE 14 : 2-[1-(Dimethylamino)cyclopropyl]ethyl dimethylcarbamate fumarate

A solution, at 5°C, of 1.3 g of the compound of Preparation H in 25 ml of tetrahydrofuran, to which is added 0.4 g of sodium hydride, is stirred for 10 minutes at 5°C, for 1 hour at ambient temperature and then for 2 hours at 40°C and is finally brought to 5°C. 1.2 g of dimethylcarbamoyl chloride are then added slowly and the reaction mixture is stirred for 1 hour at 5°C, for 1 hour at ambient temperature and then for 7 hours at 40°C and is finally concentrated under reduced pressure. The residue is taken up in dichloromethane, washed with saturated sodium chloride solution, dried and concentrated. Chromatography over silica gel (ethyl acetate) allows the expected product to be isolated, which is converted into its fumarate form in conventional manner.

Melting point : 148-149°C

Elemental microanalysis :

	C	H	N
% calculated	**53.15**	**7.65**	**8.86**
% found	**52.71**	**7.52**	**8.56**

EXAMPLE 15 : 2-[1-(Dimethylamino)cyclopropyl]ethyl methylcarbamate fumarate

0.63 g of methyl isocyanate is added to a solution, cooled to 5°C, of 1.3 g of the compound of Preparation H in 26 ml of ether, and the mixture is then heated at reflux for 4 hours. The additions of methyl isocyanate are repeated three times, alternating with periods of refluxing of 4 hours. After the reaction has ceased, the mixture is concentrated under reduced pressure. Chromatography of the residue over silica gel (dichloromethane/ methanol : 95/5) allows the expected product to be isolated, which is converted into its fumarate form according to a conventional procedure.

Melting point : 118-119°C

Elemental microanalysis :

	C	H	N
% calculated	**51.65**	**7.33**	**9.27**
% found	**51.67**	**7.38**	**9.08**

EXAMPLE 16 : [1-(Dimethylamino)cyclopropyl]methyl nicotinate hydrochloride

A solution of 0.9 g of nicotinic acid chloride hydrochloride, 0.76 g of the compound of Preparation F and 0.06 g of 4-dimethylaminopyridine in 15 ml of pyridine is heated at 80°C for 5 hours and is then concentrated under reduced pressure. The residue is taken up in a mixture of ether and saturated $NaHCO_3$ solution. The organic phase is treated in conventional manner and is then concentrated. Chromatography over silica gel (dichloromethane/methanol : 97/3) allows the product to be isolated, which is converted into its hydrochloride form in conventional manner.

Melting point : > 130°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	**45.01**	**6.61**	**8.75**	**22.14**
% found	**45.06**	**6.70**	**8.61**	**21.03**

EXAMPLE 17 : *N,N*-Dimethyl-1-[(3-pyridylmethoxy)methyl]cyclopropanamine hydrochloride

1.32 g of sodium hydride are added to a solution of 3.4 g of the compound of Preparation F in 55 ml of dimethylformamide. The reaction mixture is held at 45°C for 1 hour 30 minutes and is then brought to ambient temperature before being cooled to 0°C; 0.036 mol of 3-picolyl chloride is added. The reaction mixture is stirred for 16 hours at ambient temperature followed by 5 hours at 50°C, and is then concentrated under reduced pressure. The residue is taken up in saturated sodium carbonate solution and is then extracted with ethyl acetate. The organic phase is treated in conventional manner and evaporated. Chromatography of the residue over silica gel (dichloromethane/methanol : 97.5/2.5)

allows the expected product to be isolated, which is converted into its hydrochloride in conventional manner.

Melting point : 205-210°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	**51.62**	**7.22**	**10.03**	**25.40**
% found	**51.72**	**7.22**	**9.78**	**25.46**

EXAMPLE 18 : *N*-Methyl-1-[(3-pyridyloxy)methyl]cyclopropanamine hydrochloride

Step 1 : *tert*-Butyl *N*-methyl-{1-[(3-pyridyloxy)methyl]cyclopropyl}carbamate

4.7 ml of diethyl azodicarboxylate are added to a solution, cooled to 0°C, of 7.9 g of triphenylphosphine in 80 ml of tetrahydrofuran. After 45 minutes, the reaction mixture is brought to ambient temperature and 2.9 g of 3-hydroxypyridine and 4 g of the compound of Preparation I suspended in 40 ml of tetrahydrofuran are added. After stirring for 24 hours, the mixture is concentrated under reduced pressure and then 100 ml of 1N hydrochloric acid are added. The aqueous phase is extracted with ethyl acetate, made alkaline by the addition of solid potassium carbonate and re-extracted with ether. The combined organic phases are treated in customary manner and then evaporated. Chromatography over silica gel (dichloromethane/tetrahydrofuran : 97/3) allows the expected product to be isolated.

Step 2 : *N*-Methyl-1-[(3-pyridyloxy)methyl]cyclopropanamine hydrochloride

A solution containing 0.32 g of the compound obtained in Step 1 in 3 ml of dioxane and 3 ml of 4N hydrochloric acid in dioxane is stirred for 1 hour at ambient temperature and under an inert atmosphere, and is then diluted with ether. The liquid phase is then separated off and the residue is taken up in 25 ml of ethanol. The solution is concentrated to 2 ml and is then diluted with 20 ml of ether and stirred; the precipitate formed is filtered off, rinsed and dried, allowing the expected product to be isolated.

Melting point : 152-155°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	**46.82**	**6.52**	**10.92**	**27.64**
% found	**46.83**	**6.48**	**10.68**	**27.68**

EXAMPLE 19 : *N,N*-Dimethyl-1-[(3-pyridyloxy)methyl]cyclopropanamine hydrochloride

1.07 g of the compound of Example 18 diluted with 1.2 ml of water are added to a solution, cooled to 0°C, of 1.38 g of formic acid, 1.12 ml of 37 % formaldehyde in water and 0.15 ml of distilled water. The reaction mixture is heated at reflux for 16 hours and is then cooled to 0°C and 10 ml of 4N sodium hydroxide solution are added. The mixture is extracted with ether. The organic phase is treated in customary manner and evaporated. The residue is taken up in ethanol, concentrated again and then diluted with 20 ml of ether and 4 ml of 4N hydrochloric acid solution in dioxane. The mixture is stirred for 20 minutes, filtered, rinsed with ether and dried, allowing the expected product to be isolated.

Melting point : 215-220°C

EXAMPLE 20 : *N,N*-Dimethyl-1-[2-(3-pyridyloxy)ethyl]cyclopropanamine dihydrochloride

A solution containing 0.58 g of 3-hydroxypyridine sodium salt in 5 ml of dimethyl sulphoxide and 0.46 g of the compound of Preparation J is heated at reflux for 16 hours and is then brought to ambient temperature and taken up in a mixture of ether/saturated sodium carbonate solution. After being separated off, the aqueous phase is extracted with ethyl acetate and the organic phases are then washed with 1N sodium hydroxide solution and then with 10 % lithium chloride solution. After concentration, the residue is taken up in 20 ml of ether and the dihydrochloride of the expected product is obtained in conventional manner.

Melting point : 173-175°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	**50.75**	**7.31**	**11.34**	**24.97**
% found	**50.76**	**7.28**	**9.72**	**24.37**

EXAMPLE 21 : 4-({2-[1-(Dimethylamino)cyclopropyl]ethyl}sulphanyl)phenol hydrochloride

A solution containing 0.4 g of 90 % 4-hydroxythiophenol, 0.46 g of the compound of Preparation J in 10 ml of dimethylformamide and 0.7 g of potassium carbonate is stirred for 24 hours at ambient temperature and is then diluted with ether. The mixture is acidified by the addition of 15 ml of 1N hydrochloric acid and is then separated. The organic phase is re-extracted with 15 ml of 1N hydrochloric acid and the aqueous phases are made alkaline and extracted with ethyl acetate. After drying of the acetylated phases and concentration thereof, the residue obtained corresponds to the expected product, which is converted into its hydrochloride form in conventional manner.

Melting point : 193-195°C

PHARMACOLOGICAL STUDIES OF COMPOUNDS OF THE INVENTION

EXAMPLE 22 : Displacement of binding of [^{125}I]-α-bungarotoxin on nicotinic receptors of the electric organ of torpedo fish

This study, carried out according to the method of Sullivan *et al.* (J. Pharmacol. Exp. Ther., 1994, 271 ; 624-631), is aimed at assessing the affinity of compounds of the present invention for nicotinic receptors of the "muscular" type.

Membranes (1-5 µg/ml) of the electric organ of torpedo fish are incubated (1 hour, 22°C) in the presence of a series of concentrations (0.01-10 µM) of each compound of the invention (diluted starting from a 10 mM stock solution in DMSO) in the presence of [^{125}I]-α-bungarotoxin (S.A. : 7.4 TBq/mmol : 0.2 nM) in Krebs buffer (Tris-HCl 50 mM, KCl 5 mM, $MgCl_2$ 1 mM, $CaCl_2$ 2 mM, NaCl 100 mM, pH 7.4) with 0.01 % BSA; final

volume: 500 µl. The non-specific binding is determined by incubating membranes in the presence of α-bungarotoxin (1 µM).

The results show that, up to a concentration of 10 µM, the compounds of the present invention have no significant affinity for nicotinic receptors of the "muscular" type.

EXAMPLE 23 : Displacement of binding of [^{3}H]-epibatidine on nicotinic receptors of IMR32 cells

This study, carried out according to the technique of Houghtling *et al.* (Molec. Pharmacol., 1995, 48 ; 280-287), is aimed at determining the affinity of compounds of the present invention for nicotinic receptors of the "ganglionic" type (Lockhart *et al.*, American Soc. Neuroscience, 2000, at press).

Membranes (250 µg/ml) of IMR-32 neuroblastoma cells are incubated (2 hours, 20°C) in the presence of a series of concentrations (0.01-10 µM) of each compound of the invention (diluted starting from a 10 mM stock solution in DMSO) and (±)-[^{3}H]-epibatidine (S.A. : 2464 GBq/mmol : 1.5 nM) in phosphate buffer (NaH_2PO_4 20 mM, pH 7.4); final volume: 250 µl. The non-specific binding is determined by incubating membranes in the presence of 300 µM of (-)nicotine.

The results show that, up to a concentration of 10 µM, the compounds of the present invention have no significant affinity for nicotinic receptors of the "ganglionic" type.

EXAMPLE 24 : Displacement of binding of [^{3}H]-oxotremorine-M on muscarinic receptors of rat brain

This study, carried out according to the method of Lockhart *et al.* (Naumyn-Schmieder-berg's Arch. Pharmacol., 2000, at press), is aimed at determining the affinity of compounds of the present invention for muscarinic receptors.

Membranes (250 µg/ml) of rat brain are incubated (2 hours, 20°C) in the presence of a series of concentrations (0.01-10 µM) of each compound of the invention (diluted starting from a 10 mM stock solution in DMSO) and [^{3}H]-oxotremorine-M (S.A. : 3174 GBq/mmol : 2 nM) in phosphate buffer (NaH_2PO_4 20 mM, pH 7.4); final volume: 250 µl. The specific binding is determined by incubating membranes in the presence of

atropine (1 μM). The affinity of the compounds of the present invention for muscarinic receptors is characterised by determination of the K_i.

The results show that, up to a concentration of 10 μM, most of the compounds of the present invention have no affinity for muscarinic receptors. Certain compounds of the invention have a K_i of the order of 10 μM.

EXAMPLE 25 : Displacement of binding of [^{125}I]-α-bungarotoxin on "type α7" nicotinic receptors of rat brain

This study, carried out according to the method described by Marks *et al.* (Molec. Pharmacol., 1986, 30 ; 427-436), is aimed at determining the affinity of compounds of the present invention for type α7 central nicotinic receptors.

Membranes (1000 μg/ml) of rat brain are incubated (5 hours, 37°C) in the presence of a series of concentrations (0.01-10 μM) of each compound of the present invention (diluted starting from a 10 mM stock solution in DMSO) and [^{125}I]-α-bungarotoxin (S.A. : 7.4 TBq/mmol : 1 nM) in Krebs buffer (Tris-HCl 50 mM, KCl 5 mM, $MgCl_2$ 1 mM, $CaCl_2$ 2 mM, NaCl 100 mM, pH 7.4) with 0.05 % BSA; final volume: 500 μl. The non-specific binding is determined by incubating membranes in the presence of α-bungarotoxin (1 μM).

The affinity of compounds of the present invention for type α7 nicotinic receptors is characterised by determination of the K_i.

The results show that, up to a concentration of 10 μM, most of the compounds of the present invention have no affinity for type α7 central nicotinic receptors. Certain compounds of the invention have a K_i of the order of 10 μM.

EXAMPLE 26 : Displacement of binding of [^{3}H]-cytisine on "type α4β2" nicotinic receptors of rat brain

This study, carried out according to the technique of Pabreza *et al.* (Molec. Pharmacol., 1990, 39 ; 9-12), is aimed at determining the affinity of compounds of the present invention for type α4β2 central nicotinic receptors.

Membranes (250 μg/ml) of rat brain are incubated (2 hours, 20°C) in the presence of a series of concentrations (0.01-10 μM) of each compound of the present invention (diluted

starting from a 10 mM stock solution in DMSO) and [^{3}H]-cytisine (S.A. : 1184 GBq/mmol : 2 nM) in phosphate buffer (NaH_2PO_4 20 mM, pH 7.4); final volume: 250 µl. The non-specific binding is determined by incubating membranes in the presence of 10 µM of (-)nicotine. The affinity of the compounds of the present invention for type α4β2 central nicotinic receptors is characterised by determination of the K_i.

The results obtained show that the compounds of the present invention have a strong affinity for type α4β2 central nicotinic receptors with K_i values of the order of 10-100 nM.

These results, and also those obtained in Examples 22 to 25, show that the compounds of the present invention are powerful central nicotinic ligands that are specific to type α4β2 receptors.

EXAMPLE 27 : Pharmaceutical compositions for 1000 tablets each containing 10 mg of active ingredient

Compound of Example 18	10 g
Hydroxypropyl methylcellulose	10 g
Wheat starch	15 g
Lactose	90 g
Magnesium stearate	2 g

CLAIMS

1- Compounds of formula (I) :

(I),

wherein :

p represents an integer of from 0 to 6 inclusive,

n represents an integer of from 0 to 6 inclusive,

R_1 and R_2, which may be identical or different, each independently of the other represent a group selected from a hydrogen atom, a linear or branched (C_1-C_6)alkyl group, an aryl group and an aryl-(C_1-C_6)alkyl group in which the alkyl moiety is linear or branched, or R_1+R_2 form together with the nitrogen atom carrying them a saturated, monocyclic or bicyclic (C_3-C_{10}) system, one of the carbon atoms of which is optionally replaced by a hetero atom selected from oxygen, nitrogen and sulphur,

X represents a group selected from an oxygen atom, a sulphur atom, a methylene group, a group of formula -HC=N-O- and a group of formula -O-CH_2-CH=CH-, in which groups the oxygen atom is linked to the Y moiety of the compounds of formula (I),

Y represents a group selected from aryl, heteroaryl, aryl-(C_1-C_6)alkyl in which the alkyl moiety is linear or branched, heteroaryl-(C_1-C_6)alkyl in which the alkyl moiety is linear or branched, -C(O)-A and -C(S)-A,

A represents a group selected from linear or branched (C_1-C_6)alkyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl in which the alkyl moiety is linear or branched, heteroaryl-(C_1-C_6)alkyl in which the alkyl moiety is linear or branched, and NR_3R_4 wherein R_3 and R_4, which may be identical or different, each represent a group selected from a hydrogen atom, a linear or branched (C_1-C_6)alkyl group, an aryl group and an aryl-(C_1-C_6)alkyl group in which the alkyl moiety is linear or branched, or R_3+R_4 form together with the nitrogen atom carrying them a monocyclic or bicyclic (C_3-C_{10}) system,

their isomers and addition salts thereof with a pharmaceutically acceptable acid or base,

with the proviso that :

• *in the case of 1,1-disubstituted compounds of formula (I)*,

- p is other than zero when X represents a methylene group, n has the value zero, Y represents an aryl or heteroaryl group, and R_1 and R_2, which may be identical or different, represent a hydrogen atom, a linear or branched (C_1-C_4)alkyl group, a benzyl group, a phenylethyl group, or form together with the nitrogen atom carrying them a morpholino group, a thiomorpholino group or a 5- to 7-membered saturated carbocyclic system,
- p is other than zero when X represents a methylene group, n has the value zero, Y represents an acetyl group, and R_1 and R_2, which may be identical or different, represent a hydrogen atom, a linear or branched (C_1-C_4)alkyl group, a phenyl group, a benzyl group, or form together with the nitrogen atom carrying them a piperidyl or morpholino group,
- R_1 and R_2 do not simultaneously represent a methyl group :
  * either when p and n each have the value 1, X represents an oxygen atom and Y represents a group selected from p-nitrobenzoyl, p-aminobenzoyl, p-chlorophenyl-aminocarbonyl or acetyl,
  * or when p has the value zero, n has the value 1, X represents an oxygen atom or a sulphur atom and Y represents a 2-quinolyl group substituted in the 3-position by a linear or branched (C_3-C_4)alkyl group, or a phenyl group,
- Y does not represent a 1,2-benzisoxazol-3-yl group when n has the value 1, p has the value zero and X represents an oxygen atom,

• *in the case of 1,2-disubstituted compounds of formula (I)*, R_1 and R_2 do not simultaneously represent a hydrogen atom when p and n each have the value zero and X-Y together represent a phenoxy group (optionally substituted by a methoxy group, a dimethylamino group, a fluorine atom or by one or two identical groups selected from a chlorine atom and a methyl group), a phenylsulphanyl group or a benzyloxy group,

and also with the proviso that the compounds of formula (I) are other than the following compounds :

- (1-benzylcyclopropyl)methanamine,
- 2-(benzyl)cyclopropanamine,
- 2-(phenoxycyclopropyl)methanamine,

- 2-(phenoxymethyl)-cyclopropanamine,
- (N,N-dimethyl)-2-(phenylsulphanyl)cyclopropanamine,
- (N,N-dimethyl)-2-(acetoxymethyl)-cyclopropanemethanamine,
- N,N-dimethyl-2-phenoxycyclopropanamine,
- 1-aminocyclopropyl carbonate,

it also being understood that :

- an aryl group denotes a phenyl, biphenyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, indanyl or indenyl group, each of those groups being optionally substituted by one or more identical or different groups selected from halogen atoms, linear or branched (C_1-C_6)alkyl, hydroxy, cyano, nitro, linear or branched (C_1-C_6)alkoxy, linear or branched (C_2-C_7)acyl, linear or branched (C_1-C_6)alkoxycarbonyl, linear or branched (C_1-C_6)trihaloalkyl and linear or branched (C_1-C_6)trihaloalkoxy groups and amino groups (optionally substituted by one or two linear or branched (C_1-C_6)alkyl groups),

- a heteroaryl group denotes a 5- to 12-membered, monocyclic aromatic or bicyclic system containing from one to three identical or different hetero atoms selected from oxygen, nitrogen and sulphur, one of the rings of which, in the case of a bicyclic system, is aromatic in character, and the other ring of which may be aromatic or partially hydrogenated, each of those groups being optionally substituted by one or more identical or different groups selected from the substituents defined hereinbefore for an aryl group.

2- Compounds of formula (I) according to claim 1, characterised in that n is an integer of from 0 to 2 inclusive, their isomers and addition salts thereof with a pharmaceutically acceptable acid or base.

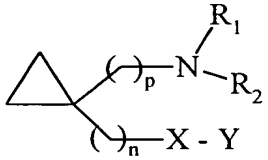
3- Compounds of formula (I) according to claim 1, characterised in that R_1 and R_2, which may be identical or different, each represent a hydrogen atom or a linear or branched (C_1-C_6)alkyl group, their isomers and addition salts thereof with a pharmaceutically acceptable acid or base.

4- Compounds of formula (I) according to claim 1, characterised in that X represents an oxygen atom, their isomers and addition salts thereof with a pharmaceutically acceptable acid or base.

5- Compounds of formula (I) according to claim 1, characterised in that Y represents a group selected from $-C(O)NR_3R_4$ wherein R_3 and R_4 are as defined for formula (I), acetyl, -C(O)-heteroaryl, aryl-$(C_1$-$C_6)$alkyl in which the alkyl moiety is linear or branched, and heteroaryl, their isomers and addition salts thereof with a pharmaceutically acceptable acid or base.

6- Compounds of formula (I) according to claim 1, characterised in that Y represents a pyridyl group, their isomers and addition salts thereof with a pharmaceutically acceptable acid or base.

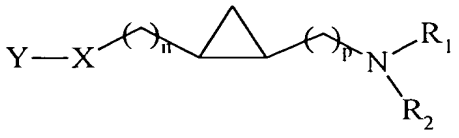
7- Compounds of formula (I) according to claim 1, characterised in that they represent compounds of formula **(IA)** :



(IA),

wherein n, p, X, Y, R_1 and R_2 are as defined for formula (I), their isomers and addition salts thereof with a pharmaceutically acceptable acid or base.

8- Compounds of formula (I) according to claim 1, characterised in that they represent compounds of formula **(IB)** :



(IB),

wherein n, p, X, Y, R_1 and R_2 are as defined for formula (I), their isomers and addition salts thereof with a pharmaceutically acceptable acid or base.

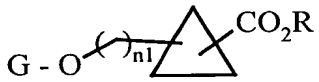
9- Compounds of formula (I) according to claim 1, characterised in that p is an integer having the value 0 or 1, their isomers and addition salts thereof with a pharmaceutically acceptable acid or base.

10- Compounds of formula (I) according to claim 1, which are :

- 2-[1-(dimethylamino)cyclopropyl]ethyl methylcarbamate,
- 2-[1-(dimethylamino)cyclopropyl]ethyl dimethylcarbamate,
- [1-(dimethylamino)cyclopropyl]methyl dimethylcarbamate,
- [1-(dimethylamino)cyclopropyl]methyl acetate,
- 2-[1-(dimethylamino)cyclopropyl]ethyl acetate,
- 1-[(dimethylamino)methyl]cyclopropyl acetate,
- [1-(dimethylamino)cyclopropyl]methyl nicotinate,
- *N*,*N*-dimethyl-1-[(3-pyridyloxy)methyl]cyclopropanamine,
- *N*-methyl-1-[(3-pyridyloxy)methyl]cyclopropanamine,
- *N*,*N*-dimethyl-1-[(3-pyridylmethoxy)methyl]cyclopropanamine,
- *N*,*N*-dimethyl-1-[2-(3-pyridyloxy)ethyl]cyclopropanamine,
- 4-({2-[1-dimethylamino)cyclopropyl]ethyl}sulphanyl)phenol,
- (±)-*cis*-2-(dimethylamino)cyclopropyl methylcarbamate,
- (±)-*trans*-2-(dimethylamino)cyclopropyl methylcarbamate,
- (±)-*cis*-2-(dimethylamino)cyclopropyl acetate,
- (±)-*trans*-2-(dimethylamino)cyclopropyl acetate,
- (±)-*cis*-2-(dimethylamino)cyclopropyl]methyl acetate,
- (±)-*trans*-2-(dimethylamino)cyclopropyl]methyl acetate,
- (±)-*cis*-2-[(benzyloxy)methyl]-*N*,*N*-dimethylcyclopropanamine,
- (±)-*trans*-2-[(benzyloxy)methyl]-*N*,*N*-dimethylcyclopropanamine, and
- (±)-*trans*-2-[(dimethylamino)methyl]cyclopropyl acetate,

their isomers and addition salts thereof with a pharmaceutically acceptable acid or base.

11- Process for the preparation of compounds of formula (I), characterised in that there is used as starting material a compound of formula **(II)** :

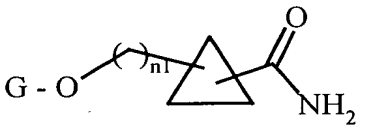


(II),

wherein G represents a protecting group conventionally used in organic synthesis, R represents a hydrogen atom or a linear or branched (C_1-C_6)alkyl group, and n_1 represents 0 or 1,

which compounds of formula (II) are :

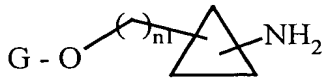
✶ ***either*** reacted with liquid ammonia in the presence of an alkali metal cyanide in an alcoholic solvent to yield the compounds of formula **(III)** :



(III),

wherein G represents a protecting group for hydroxy functions and n_1 represents 0 or 1,

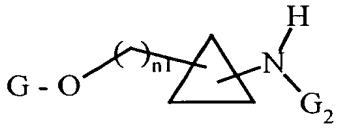
which compounds of formula (III) are treated with a dihalide in the presence of a base such as sodium hydroxide to yield the compounds of formula **(IV)** :



(IV),

wherein G and n_1 are as defined hereinbefore,

the primary amine function of which compounds of formula (IV) is selectively protected by a protecting group G_2 customarily used in organic chemistry such as the group BOC (t-butoxycarbonyl) to yield the compounds of formula **(V)** :



(V),

wherein n_1, G and G_2 are as defined hereinbefore,

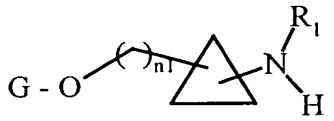
which compounds of formula (V) are then successively :

- treated, in a basic medium, with a compound of formula **(VIA)** :

$$R_1 - L_1 \qquad \textbf{(VIA),}$$

wherein R_1 is as defined for formula (I) and L_1 represents a customary leaving group of organic synthesis,

• the amine function of which is then deprotected, which compounds either undergo no further treatment and consequently yield compounds of formula **(VIIA)** :



(VIIA),

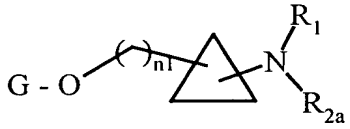
wherein R_1, n_1 and G are as defined hereinbefore,

or are reacted with a compound of formula **(VIB)** :

$$R_{2a} - L_1 \qquad \textbf{(VIB),}$$

wherein R_{2a} has the same meanings as R_2 as defined for formula (I) except for the meaning of a hydrogen atom and L_1 is as defined hereinbefore,

to yield compounds of formula **(VIIB)** :



(VIIB),

wherein R_1, R_{2a}, n_1 and G are as defined hereinbefore,

the totality of the compounds of formulae (VIIA) and (VIIB) forming the compounds of formula **(VII)** :

(VII),

wherein n_1, G, R_1 and R_2 are as defined hereinbefore,

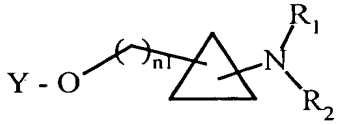
the hydroxy function of which compounds of formula (VII) is deprotected, which compounds are then :

♦ **<u>either</u>** treated with a compound of formula **(VIII)** :

$$Y - L_1 \qquad \textbf{(VIII),}$$

wherein Y is as defined for formula (I) and L_1 is as defined hereinbefore,

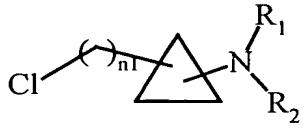
to yield compounds of formula **(I/a)**, a particular case of the compounds of formula (I) :



(I/a),

wherein n_1, Y, R_1 and R_2 are as defined for formula (I),

♦ **or** reacted with $SOCl_2$ to yield compounds of formula **(IX)** :



(IX),

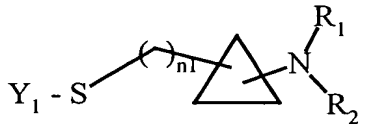
wherein n_1, R_1 and R_2 are as defined hereinbefore,

which compounds of formula (IX) are reacted, in a basic medium, with a compound of formula **(X)** :

$$Y_1 - SH \qquad \textbf{(X)},$$

wherein Y_1 represents an aryl group, an aryl-(C_1-C_6)alkyl group in which the alkyl moiety is linear or branched, a heteroaryl group or a heteroaryl-(C_1-C_6)alkyl group in which the alkyl moiety is linear or branched,

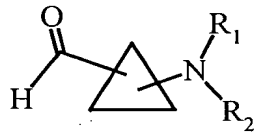
to yield compounds of formula **(I/b)**, a particular case of the compounds of formula (I) :



(I/b),

wherein Y_1, n_1, R_1 and R_2 are as defined hereinbefore,

♦ **or**, when n_1 has the value 1, subjected to the action of a conventional oxidising agent of organic synthesis to yield compounds of formula **(XI)** :



(XI),

wherein R_1 and R_2 are as defined hereinbefore,

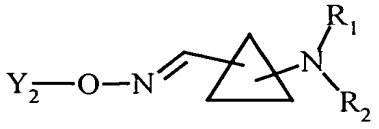
which compounds of formula (XI) are :

↳ *either* treated with a hydroxylamine of formula **(XII)** :

$$H_2N - OY_2 \qquad \textbf{(XII)},$$

wherein Y_2 represents a hydrogen atom or a group Y_1 as defined hereinbefore,

to yield compounds of formula **(I/c)**, a particular case of the compounds of formula (I) :



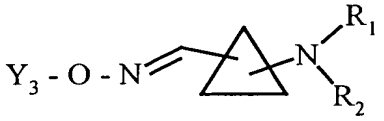
(I/c),

wherein Y_2, R_1 and R_2 are as defined hereinbefore,

which compounds of formula (I/c), in the particular case where Y_2 represents a hydrogen atom, are subjected to the action of a compound of formula **(XIV)** :

$$Y_3 - L_1 \qquad \textbf{(XIV)},$$

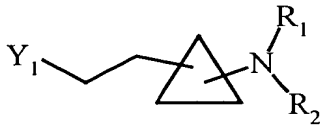
wherein L_1 is as defined hereinbefore and Y_3 represents a group of formula -C(O)-A or -C(S)-A as defined for formula (I), to yield compounds of formula **(I/d)**, a particular case of the compounds of formula (I) :



(I/d),

wherein Y_3, R_1 and R_2 are as defined hereinbefore,

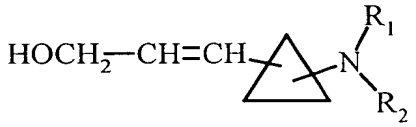
↳ *or* treated under Wittig reaction conditions and then subjected to the action of a customary reducing agent of organic synthesis to yield compounds of formula **(I/e)**, a particular case of the compounds of formula (I),



(I/e),

wherein Y_1, R_1 and R_2 are as defined hereinbefore,

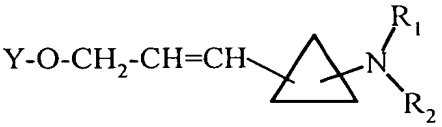
↳ *or* subjected to the action of a compound of formula $Ph_3P{=}CH\text{-}CO_2Et$ and then reduced by the action of a reducing agent of organic synthesis to yield compounds of formula **(XV)** :



(XV),

wherein R_1 and R_2 are as defined hereinbefore,

which compounds of formula (XV) are treated with a compound of formula (VIII) as defined hereinbefore to yield compounds of formula **(I/f)**, a particular case of the compounds of formula (I) :



(I/f),

wherein Y, R_1 and R_2 are as defined for formula (I),

♦ **or**, when n_1 has the value 1, converted into their corresponding halogenated derivative under customary conditions of organic chemistry and then reacted with an alkali metal cyanide in the presence of dimethyl sulphoxide to yield compounds of formula **(XVI)** :

(XVI),

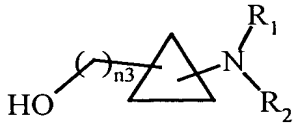
wherein R_1 and R_2 are as defined hereinbefore,

which compounds of formula (XVI) are converted into an ester under conventional conditions and then subjected to a reducing agent to yield compounds of formula **(XVIIA)** :

(XVIIA),

wherein R_1 and R_2 are as defined hereinbefore,

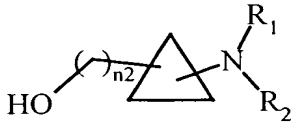
which compounds of formula (XVIIA) may be subjected again to the same series of reactions that yielded the compounds of formulae (XVI) and (XVII) to yield compounds of formula **(XVIIB)** :



(XVIIB),

wherein R_1 and R_2 are as defined hereinbefore and n_3 is an integer of from 3 to 6 inclusive,

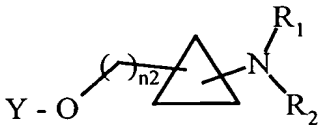
the totality of the compounds of formulae (XVIIA) and (XVIIB) forming the compounds of formula **(XVIII)** :



(XVIII),

wherein R_1 and R_2 are as defined hereinbefore and n_2 is an integer of from 2 to 6 inclusive,

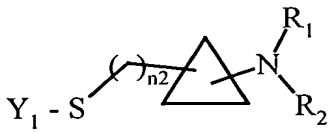
↳ *either* reacted with a compound of formula Y-L_1 as described hereinbefore to yield compounds of formula **(I/g)**, a particular case of the compounds of formula (I) :



(I/g),

wherein Y, n_2, R_1 and R_2 are as defined hereinbefore,

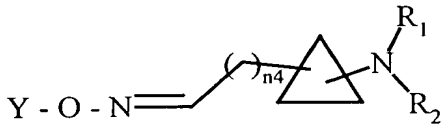
↳ *or* reacted with $SOCl_2$ and then treated with a compound of formula (X) as described hereinbefore to yield compounds of formula **(I/h)**, a particular case of the compounds of formula (I),



(I/h),

wherein Y_1, n_2, R_1 and R_2 are as defined hereinbefore,

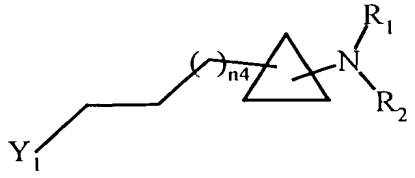
↳ *or* subjected to the action of an oxidising agent, the aldehyde intermediate obtained then being reacted with a hydroxylamine of formula (XII) as described hereinbefore and wherein Y_2 specifically represents a hydrogen atom and then, if desired, the compounds obtained are subjected to the action of a compound of formula (XIV) as described hereinbefore to yield compounds of formula **(I/i)**, a particular case of the compounds of formula (I) :



(I/i),

wherein R_1, R_2 and Y are as defined for formula (I) and n_4 represents an integer having a value of (n_2-1) wherein n_2 is as defined hereinbefore,

↳ *or* treated, after the action of an oxidising agent, under Wittig reaction conditions and then treated under conventional reduction conditions of organic synthesis to yield compounds of formula **(I/j)**, a particular case of the compounds of formula (I) :



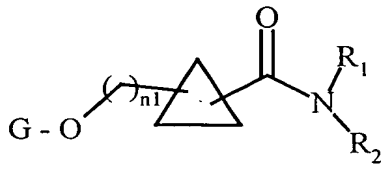
(I/j),

wherein Y_1, n_4, R_1 and R_2 are as described hereinbefore,

✶ ***or*** reacted in the presence of Me_3Al in a non-polar solvent with a compound of formula **(XIX)** :

$$HNR_1R_2 \qquad \textbf{(XIX)},$$

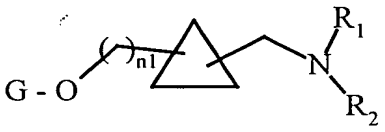
wherein R_1 and R_2 are as defined for formula (I), to yield compounds of formula **(XX)** :



(XX),

wherein n_1, G, R_1 and R_2 are as defined hereinbefore,

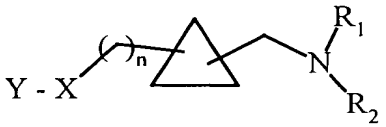
which compounds of formula (XX) are subjected to the action of a reducing agent conventionally used in organic synthesis, to yield the compounds of formula **(XXI)** :



(XXI),

wherein G, n_1, R_1 and R_2 are as defined hereinbefore,

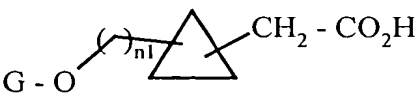
which compounds of formula (XXI) may be subjected to the totality of reactions to which the compounds of formula (VII) are subjected, to yield compounds of formula **(I/k)**, a particular case of the compounds of formula (I) :



(I/k),

wherein X, Y, n, R_1 and R_2 are as defined for formula (I),

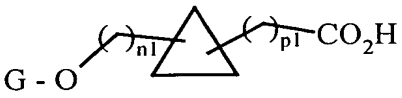
✶ ***or*** reacted with thionyl chloride, when R represents a hydrogen atom, and then placed in the presence of diazomethane in an aqueous medium to yield compounds of formula **(XXII)** :



(XXII),

wherein n_1 and G are as defined hereinbefore,

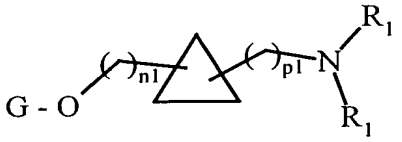
which compounds of formula (XXII) may again be subjected several times to the same reaction series to yield compounds of formula **(XXIII)** :



(XXIII),

wherein n_1 and G are as defined hereinbefore and p_1 represents an integer of from 2 to 6 inclusive,

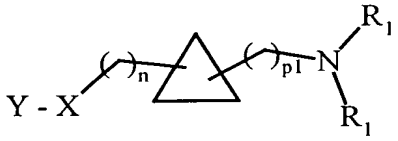
which compounds of formula (XXIII) are reacted with diphenylphosphoryl azide, hydrolysed and then treated with a compound of formula (VIA) as described hereinbefore to yield compounds of formula **(XXIV)** :



(XXIV),

wherein R_1 is as defined for formula (I) and G, n_1 and p_1 are as defined hereinbefore,

which compounds of formula (XXIV) may be subjected to the totality of reactions to which the compounds of formula (VII) are subjected, to yield compounds of formula **(I/l)**, a particular case of the compounds of formula (I) :



(I/l),

wherein X, Y, R_1 and n are as defined for formula (I) and p_1 is as defined hereinbefore,

the totality of compounds of formulae (I/a) to (I/l) constituting the totality of the compounds of the invention, which are purified, where appropriate, according to a conventional purification technique, which may be separated into their different isomers according to a conventional separation technique, and which are converted, where appropriate, into addition salts thereof with a pharmaceutically acceptable acid or base.

12- Pharmaceutical compositions comprising as active ingredient at least one compound according to any one of claims 1 to 10, alone or in combination with one or more inert, non-toxic, pharmaceutically acceptable excipients or carriers.

13- Pharmaceutical compositions according to claim 12 comprising at least one active ingredient according to any one of claims 1 to 10 for use, as a medicament, as a specific nicotinic ligand of $\alpha 4\beta 2$ receptors.

14- Pharmaceutical compositions according to claim 12 comprising at least one active ingredient according to any one of claims 1 to 10 for use, as a medicament, in the treatment of deficiencies of memory associated with cerebral ageing and with neurodegenerative diseases, and also for the treatment of mood disorders, Tourette's syndrome, attention-deficit hyperactivity syndrome, tobacco withdrawal and pain.

15- Pharmaceutical compositions according to claim 12 comprising at least one active ingredient according to any one of claims 1 to 10 for use, as a medicament, in the treatment of deficiencies of memory associated with Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease or frontal lobe and subcortical dementias.